



Medical Research
Council of Canada

Conseil de recherches
médicales du Canada



Towards
an
International
Ethic
for
Research
with
Human
Beings

Canada

89-03473/

**Towards an International Ethic
for Research with Human Beings**

**Proceedings of the International Summit Conference on Bioethics
April 5-10, 1987, Ottawa, Canada**

**Sponsored by the Medical Research Council of Canada and the
Department of National Health and Welfare**

**Medical Research Council of Canada
20th floor, Jeanne Mance Building
Tunney's Pasture
OTTAWA, ONTARIO, CANADA
K1A 0W9**

Canadian Cataloguing in Publication Data

International Summit Conference on Bioethics (4th ; 1987 ; Ottawa, Ont.)

Towards an international ethic for research with human beings : proceedings of the International Summit Conference on Bioethics, April 5-10, 1987, Ottawa, Canada

Issued also in French under title: Pour une éthique internationale en recherche sur des sujets humains.

ISBN 0-662-16408-3

DSS cat. no. MR4-1/1987E

1. Bioethics – Congresses. 2. Human experimentation in medicine – Moral and ethical aspect – Congresses. 3. Medicine – Research – Moral and ethical aspects – Congresses. 4. Medical ethics – Congresses. I. Medical Research Council (Canada). II. Canada. Health and Welfare Canada. III. Title.

QH332.I57 1988 174'.28 CIP C88-097009-X

Également disponible en français sous le titre
Pour une éthique internationale en recherche sur des sujets humains
©Minister of Supply and Services Canada 1988
Cat. No. MR4-1/1987E
ISBN: 0-662-16408-3

Table of Contents

FOREWORD	5
LIST OF CONFERENCE HOSTS, DELEGATES AND PERSONNEL	7
AGENDA	13
OPENING SESSION	17
BACKGROUND PAPER	25
SESSION REPORTS	35
CLOSING SESSION	55
SUMMARY REPORT	59
PRESS CONFERENCE	67
APPENDIX 1: RESUMES OF THE DELEGATES	79
ORDER FORM: PAPERS AND DISCUSSANTS' COMMENTS	82



Foreword

The fourth Bioethics Summit Conference took place in Ottawa on April 5-10, 1987. Twenty six leading authorities, nominated by the heads of state of the Economic Summit nations, by the European Economic Community, and by the World Health Organization, worked together "Towards an International Ethic for Research with Human Beings."

Research with human subjects is essential to promote health and treat disease. The need for this research raises ethical questions, particularly with respect to the risks for the subjects of research. Society has developed public policies to define acceptable directions and limits for health sciences research, limits which balance competing ethical claims.

Delegates focussed on the guiding principles and practices of these public policies. They made recommendations to improve the protection of subjects of research throughout the world. A unanimous conclusion was the importance of public participation in the decisions and the need for public dialogue.

The Medical Research Council of Canada is publishing this summary volume, as well as the formal presentations, in order to encourage the active participation and discussion by all involved or interested in research with human subjects.

This conference would not have been possible without the work of many people, the steering committee, the Ottawa-based science attaches of the Economic Summit nations, the conference personnel, the secretariat who helped prepare the summary report during the deliberations, and, above all, the delegates who shared their knowledge and experience.

This report is offered in the hope of a continuing positive impact on standards and directions for research with human subjects.



List of Conference Hosts, Delegates and Personnel

Conference Hosts

The Very Honourable Jeanne Sauvé
Governor General of Canada

The Right Honourable Brian Mulroney
Prime Minister of Canada

The Honourable Donald F. Mazankowski
Deputy Prime Minister of Canada

The Honourable Jake Epp
Minister
National Health and Welfare

The Honourable Flora MacDonald
Minister of Communications

Dr. Maureen Law
Deputy Minister
National Health and Welfare

Dr. Pierre Bois
President
Medical Research Council

Conference Delegates*

Canada:

The Hon. Mr. Justice T. David Marshall (Conference chairman)
The Supreme Court of the Northwest Territories
Yellowknife, Northwest Territories

Dr. Henry Friesen
Chairman, Dept. of Physiology
University of Manitoba
Winnipeg, Manitoba

Prof. Abbyann Lynch
Director
Westminster Institute for Ethics and Human Values
London, Ontario

European Economic Community:

Dr. Paolo Fasella
Director General for Science, Research and Development
Commission of the European Communities
Brussels, Belgium

Dr. Evangelos Garelis
Vice President, National Drug Organization of Greece
Athens General Hospital

Prof. Per Juul
Royal Danish School of Pharmacy
Dept. of Pharmacology
University of Copenhagen
Copenhagen, Denmark

Federal Republic of Germany:

Prof. Albin Eser
Director
Max Planck Institute for Foreign and International Penal Law
Freiburg

Prof. Gustav-Adolf Martini
Director of Marburg University Clinic

* Resumes of delegates in Appendix 1.

Prof. Gunther Patzig
Vice President, Academy of Sciences, Göttingen
Director, Institute of Philosophy
Georg August Universität

France:

Dr. André Boué
Professeur, Faculté de Médecine de Paris

Dr. Henri Bricaire
Professeur, Faculté de Médecine de Paris
Membre de l'Académie de Médecine

M. Jean Michaud
Membre du Comité National d'Ethique
Conseiller à la Cour de Cassation
Paris

Italy:

Dr. Liborio Falanga
Ufficio Studi e Legislazione
Ministero della Sanita
Rome

Monsignor Elio Sgreccia
Director of Bioethics Centre
Policlinico Gemelli
Universita Cattolica
Rome

Prof. Vittorio Sgaramella
Professor of Molecular Biology
Department of Genetics and Microbiology
University of Pavia

Japan:

Prof. Koichi Bai
Faculty of Law
Tokyo Metropolitan University

Dr. Shigeaki Hinohara
President, St. Luke's College of Nursing
Tokyo

Mr. Eiji Suzuki
President, Mitsubishi Chemical Industry Ltd.
Tokyo

United Kingdom:

Prof. Gordon Dunstan
Emeritus Professor of Moral Theology
University of London and University of Exeter

Mr. John Fairclough
Chief Scientific Advisor
The Cabinet Office

Sir Raymond Hoffenberg
President
Royal College of Physicians
London

United States:

Dr. Charles McCarthy
Director, Office for Protection from Research Risks
National Institutes of Health
Bethesda, Maryland

Dr. Russel Patterson
Professor of Neurosurgery
Cornell Medical College
New York, New York

Dr. Edmund Pellegrino
Professor of Medicine and Medical Humanities
Georgetown University
Director, Kennedy Institute of Ethics
Washington, D.C.

World Health Organization:

Dr. Zbigniew Bankowski
Executive Secretary
Council for International Organizations of Medical Sciences
Geneva, Switzerland

Dr. José Barzelatto
Director of Human Reproduction Programme
World Health Organization
Geneva, Switzerland

Members of the Steering Committee

The Honourable Mr. Justice T. David Marshall (Chairman)
The Supreme Court of the Northwest Territories
Yellowknife

Dr. Henry Dinsdale
Department of Medicine
Queen's University
Kingston, Ontario

Dr. Henry Friesen
Professor and Head
Department of Physiology
University of Manitoba
Winnipeg

Dr. Ronald A. Heacock
Director General
Extramural Research Programs Directorate
Health and Welfare Canada
Ottawa, Ontario

Mme Mary Lamontagne
Vice President of the Board
Centre hospitalier
Université Laval
Québec, Québec

Dr. A.J. Liston
Assistant Deputy Minister
Health Protection Branch
Health and Welfare Canada
Ottawa, Ontario

Conference Personnel

Conference Coordinator and Proceedings Editor

Judith Miller (Medical Research Council)

Secretariat

Robert Auger (International Development Research Centre)

Bartha Knoppers (Université de Montréal)

Judith Miller (Medical Research Council)

Francis Rolleston (Medical Research Council)

Richard Wilson (International Development Research Centre)

Hospitality and Liaison

Lisette Carnell (Health and Welfare Canada)

Suzanne Descamps (Health and Welfare Canada)

Joyce Henderson (Health and Welfare Canada)

Marie Lalonde (Health and Welfare Canada)

Ann Normandin (Health and Welfare Canada)

Pirangela Pica (Health and Welfare Canada)

Secretaries

Martha Bunda (Health and Welfare Canada)

Lorraine Cléroux (Medical Research Council)

Lucie Gervais (Medical Research Council)

Maureen Knox (Health and Welfare Canada)

Bonnie Ralph (Medical Research Council)

Transportation

François Séguin (Health and Welfare Canada)

Guy Séguin (Health and Welfare Canada)

External Liaison

Ward Greenwood (External Affairs)

Doug Paterson (External Affairs)

Agenda

Sunday, April 5, P.M.

Reception, hosted by Dr. Maureen Law and Dr. Pierre Bois

Monday, April 6

I. Introduction

A. Opening

Chair: David Marshall, Canada

Presenters: The Hon. Jake Epp, Dr. Pierre Bois

B. Overview

Presenter: David Marshall

C. Underlying Principles for Biomedical Ethics Review of Research with Human Subjects

Chair: Paolo Fasella, EEC

Rapporteur: Koichi Bai, Japan

1 Guiding Principles in Biomedical Research

Presenter: Elio Sgreccia, Italy

Discussant: Gunther Patzig, Federal Republic of Germany

2 Sharing the Risks: the Management of Research

Presenter: Per Juul, EEC

Discussant: Vittorio Sgaramella, Italy

II. Development and Implementation of National Ethics Standards

D. Development of National Ethics Standards for Research with Human Subjects

Chair: Gustav-Adolf Martini, Federal Republic of Germany

Rapporteur: Charles McCarthy, United States

3 Who Sets Standards for What and How

Presenter: Paolo Fasella, EEC

Discussant: Liborio Falanga, Italy

4 The Role of the Public

Presenter: Gordon Dunstan, United Kingdom

Discussant: Abbyann Lynch, Canada

Dinner, hosted by the Honourable Jake Epp,

Minister of National Health and Welfare

Tuesday, April 7

E. Procedures in Implementing National Standards for Research with Human Subjects

Chair: Jean Michaud, France

Rapporteur: Liborio Falanga, Italy

5 Mechanisms of Ethics Review

Presenter: Raymond Hoffenberg, United Kingdom

6 Accountability of the Ethics Review Process

Presenter: Vittorio Sgaramella, Italy

Discussants for 5 & 6: Charles McCarthy, U.S.

Shigeaki Hinohara, Japan

Henry Friesen, Canada

III. Special Topics in Biomedical Ethics

F. Issues Relating to Consent

Chair: Shigeaki Hinohara, Japan

Rapporteur: Evangelos Garelis, EEC

7 Research with Those with Restricted Ability to Give Consent

Presenter: Russel Patterson, United States

Discussant: André Boué, France

8 The Question of Research with Embryos and Fetuses

Presenter: Albin Eser, Federal Republic of Germany

Discussant: Gordon Dunstan, United Kingdom

Wednesday, April 8

G. Areas of Special Concern

Chair: John Fairclough, United Kingdom

Rapporteur: Albin Eser, Federal Republic of Germany

9 Ethics Review of Pilot Studies and the Introduction of Novel Therapies

Presenter: Henry Friesen, Canada

Discussant: Evangelos Garelis, EEC

10 Ethics Issues in Industrial Research

Presenter: Eiji Suzuki, Japan

Discussant: Per Juul, EEC

11 Ethics Standards for Research across Nations and Cultures

Presenter: Zbigniew Bankowski, WHO

Discussant: Edmund Pellegrino, United States

H. Ethics of Choice of Research Topic

Chair: Vittorio Sgaramella, Italy

Rapporteur: Raymond Hoffenberg, United Kingdom

12 The Selection of Research Topics and the Effectiveness of Directed Research for International Needs

Presenter: José Barzelatto, WHO

Discussant: Henri Bricaire, France

I. Discussion of conference issues and report

Chair: David Marshall, Canada

Dinner hosted by the Deputy Prime Minister

Thursday, April 9

IV. Towards Improved Ethics Standards

J. Biomedical Research Ethics in an Interdependent World

Chair: Edmund Pellegrino, United States

Rapporteur: Henri Bricaire, France

13 *The Transferability of Systems of Ethics Review*

Presenter: Jean Michaud, France

Discussant: Koichi Bai, Japan

14 *Possibilities for Refinement and Expansion of Transnational Standards*

Presenter: Abbyann Lynch, Canada

Discussant: Gustav-Adolf Martini, Federal Republic of Germany

K. Draft reports of previous sessions

Chair: David Marshall, Canada

L. Presentation of Conference Issues and Recommendations and Adoption of Final Report

Reception hosted by her Excellency, the Governor General

Friday, April 10

M. Presentation of report

Cochairs: Dr. Maureen Law and Dr. Pierre Bois

Press conference



Opening Session

The Honourable Jake Epp: Mr. Justice Marshall, Honoured Delegates,

First, may I express to you the great pride that the Government of Canada has in welcoming you to this, the fourth in a series of Annual Pre-Summit conferences on bioethics. This series, which was started in the spring of 1983 by Prime Minister Nakasone of Japan, has already established itself as an important part of the world's increasingly strong exchanges in this area. Canada has participated actively in the three conferences so far, and is grateful not only to Japan for having initiated the series, but also to France and Germany, which hosted the second and third conferences.

The word "Bioethics" was known to only a few as little as a decade ago; it has now become a part of scientific language. Why?

I believe that the concern with bioethics springs from a growing recognition of the need to examine the effects of advances in biology and medical sciences on the individual and on society. As we gain new powers to intervene in biological processes, we must also assume increased responsibilities to exercise these powers in a fitting moral and social context. The greater our powers to effect potentially beneficial change, the greater may be our temptation to proceed with research which may benefit the many, even though it may lead to harm for the few. Pressing needs such as the rising incidence of AIDS increase the opportunities for inadvertent injury to individuals. Within this human context, we must be vigilant to preserve human dignity and to protect the well-being of those who serve as subjects of research.

Perhaps the central problem is that in seeking to use newly acquired medical and biological knowledge powers for good, we are sometimes not as aware as we might be of the harm that we might cause, for example, through forgetfulness, lack of attention to details or simple over-enthusiasm.

I believe that the work that you are undertaking in the next few days has this at its core. Deliberate harm is obviously wrong, and the full extent of public censure and legal retribution must be brought to bear against those who deliberately cause harm. However, the subject that you are addressing goes far beyond this. Your concerns, I believe, are those of prevention of harm that might arise from well intentioned and highly skilled people who are acting for the good of mankind, but who may be forgetful of the broader implications of their actions, either committed or omitted.

The ways in which a country establishes and implements guidelines for the ethics of research involving human subjects are a reflection of its own values and social structures. Because of differing local or regional political, social, religious or ethical parameters, this task is difficult enough within a country. It is far more difficult between countries, where social and cultural difference are accentuated.

The need for international standards of ethics in research that take into account both the individuality of national standards and the desirability of protecting the inalienable rights of the individual – regardless of nationality, race, age, sex or health status – cannot be denied.

Trying to define such inalienable rights is no simple task. It is, however, a task of extreme importance in today's world, where national bounds are frequently transcended by collaboration between countries, as well as by multinational companies conducting research in many countries.

The consultations in which you will be involved this week will undoubtedly assist your own nations, organizations and communities as well as other countries to arrive at international guidelines for ethics in research.

In Canada, a country which, apart from our native population, is a land of immigrants, our peoples have strong and direct paternal links to each of the countries around this table. As a matter of national policy, we seek to preserve and retain the different national characteristics of the many nations whose people have chosen to live in Canada. Thus, as we continue to define our national guidelines on the ethics of research involving human subjects, we have already sought to learn from the experiences and wisdom of other countries. We look forward to continuing this thrust this week and in the future.

Ladies and gentlemen, the subject that you will be discussing here this week is of very great concern to me personally, to this country and to the peoples of the world. The subject has already received much attention, and will rightfully continue to concern mankind for as long as we continue to want to improve our knowledge of ourselves and the world around us, while retaining respect for ourselves and, indeed, for all life.

At the first Conference on Life Sciences and Mankind, Prime Minister Nakasone remarked:

"In the final analysis, the problems center on the question of what makes man truly man, what constitutes 'human dignity' ... I believe that these problems which concern human life and human dignity should be thoroughly studied, not by scientific and technological specialists only ..."

The theme of this year's conference, "Towards an International Ethic for Research with Human Subjects," reaffirms the importance of human dignity in the wise application of advances in science and technology. I am sure from the agenda and from the excellence of the individual delegates that the discussions will be of high quality.

I am particularly pleased that you have seen fit to include a section on the role of the public in your agenda. Being from that group myself, and more importantly, representing the public, I perhaps have a vested interest in this area.

I shall learn the conclusions of your deliberations in five days time and will convey them to Prime Minister Mulroney who convened this Conference. He intends to table them for discussion at the Economic Summit Meeting in Venice, Italy. Your

work will provide an international dimension and recognition to work which has often been a more national or local undertaking.

At this time, I wish to thank all of you who have honoured Canada by coming and tackling together the difficult and important issues necessary to protect human dignity in the conduct of research.

In closing, it remains merely for me to express my confidence that you will have a productive and enjoyable meeting, and my thanks to you for your presence and participation here this week.

Dr. Pierre Bois: Mr. Chairman, Mr. Minister, distinguished guests,

Permit me to add my greetings to those expressed by the Honourable Jake Epp. The topic that you will discuss this week, which is important to us all, is particularly important for the Medical Research Council of Canada.

In Canada, as in all your nations, we hold the ethics of research as a primary element integral to the research endeavor. Thus, the Medical Research Council has concerned itself for many years with the ethical conduct of research. Our mandate is simply to "promote, assist and undertake basic, applied and clinical research in Canada in the health sciences." The Medical Research Council has no authority beyond that inherent to its mandate. Yet the MRC believes that its accountability to the public implies responsibility both for the excellence and well-being of health sciences and for the social and moral human context of such research.

The public gains from the benefits that accrue as a result of research, but it may also suffer the consequences of the risks that may be involved. Society as a whole is diminished by actions which are against societal standards, just as much as it is enhanced by praiseworthy actions.

Thus the Medical Research Council of Canada has prepared guidelines pertaining to the conduct of research. We have done so not only for the ethics of research with human subjects, but also for the processes of genetic engineering and, indirectly, for the use of animals in research. The MRC's Standing Committee on Ethics in Experimentation, led by our Conference Chairman, the Honourable Mr. Justice and Dr. David Marshall, is our central authority in these complex areas. I think it is fair to say that the MRC documents have become benchmarks for Canadian thought and practice in medical research.

The guidelines are followed not only by our grantees, for whom they are a requirement, but also by many researchers funded by other sources, be they provincial, private or industrial.

The fundamental principle which the MRC has followed in its Guidelines has been to increase the ethical sensitivity and awareness of those involved in research and to encourage control at a local level. We have offered guidance for those who must make the decisions to ask the important questions as they wrestle with the issues. We believe this is the right approach for this country, but there is always room to learn from the experience and advice of others.

The Medical Research Council is privileged to have Memoranda of Understanding and grants and awards programs to facilitate scientific exchange between Canada and other nations. Just as we have gained much from working together with other countries on research related to world health problems, we can benefit from international collaboration on the criteria and the means to conduct such research ethically.

Given our varied backgrounds...cultural, religious, political...are we able to arrive at any common standards upon which we can all agree? Can we find standards that will help us to shape and develop world health sciences according to fundamental precepts that we can all accept?

We have set ourselves a very busy and demanding program for the next five days. We shall all have to take in and digest a lot of information and to respond quickly to it. We shall have to stretch ourselves to make the greatest use of what I feel is an unusual and timely opportunity.

Before so distinguished and informed a group, I need not enumerate the problems before us. The world is faced with an epidemic of sexually transmitted diseases, with difficult questions arising from leaps in technology pertaining to reproduction and organ transplants, with fundamental queries as to the limits of the research permissible on a few to benefit the many.

The ethical challenges that we face today are unprecedented. Even as recently as fifteen years ago, we could console ourselves with the knowledge that the problems exceeded our technical skills. That is not so easy a case to make today.

Recent advances in the health sciences in the past decade are measured in quantum leaps. Our grasp in some cases ... and we cannot know in how many ... may well exceed our reach. This is almost certainly the first time in human history that we have had to face this dilemma.

Over the next several days we shall have to share our experiences, pool our knowledge, compare our insights ... in short, learn from each other.

Thank you for joining us and working with us at the International Summit Conference on Bioethics. Merci.

Mr. Justice David Marshall: I would like to add my own remarks of welcome to those of our distinguished hosts and to discuss with you our hopes for our deliberations and my suggestions as to how we might proceed in our work this week. I am looking forward to a productive week of working together, a week in which we learn from each other and share our experiences in facing the problems at the interface of science, ethics and law which arise for those who undertake research with human subjects.

It may be helpful to consider our work in terms of the stages of knowledge and learning. In early history intellectuals were generalists who studied all aspects of the world. Aristotle is an example par excellence. Natural philosophers like Isaac Newton embraced many spheres of knowledge in a period where there was little formal separation between science and philosophy. Benjamin Franklin likewise blended a curiosity and understanding of many fields. In more recent years, we have become

great specialists, vastly expanding our knowledge and expertise in many narrowly focussed areas of learning. Advances in the sciences and particularly the biosciences have tended to outstrip the rate of our progress in the understanding of how best to apply the findings for the good of society and of individuals. New capacities in genetic screening, prenatal diagnosis and organ transplants, for example, have challenged our social fabric. It seems that we are now entering a new stage of learning, heralded by the increase in multidisciplinary, team approaches and the rise in appreciation of disciplines such as biotechnology, bioethics and ecology which integrate many fields of study. The new stage is one of synthesis, where we begin to meld the specialties into a whole which may be more than the sum of its parts. It is my hope that during this week we shall each bring forward the parts of the problems of which we are most aware and build together the in-depth appreciation necessary to come to terms with the issues in human experimentation.

Perhaps you will permit me to tell you a story about a judge, a physicist and a traffic ticket. A physicist who received a ticket for driving through a red light, pleaded not guilty in court. He argued: "My Lord, there is a simple physical explanation. Because of the Doppler effect, as I approached the light, the wavelengths grew shorter and the light appeared green to me. I simply drove through a green light which is perfectly within the law." The judge, himself not being entirely foolish, said: "I too know something about physics and I convict you anyway, not for running a red light, but for speeding. For the Doppler effect to occur, you would have had to have been travelling near the speed of light."

The story is instructive for us. In our reexamination of the principles and practices of ethics review, we will have to step beyond the confines of our disciplines, be they law, biology, medicine, philosophy or social sciences.

Let me take this one step further. We are not here to try anyone for an offence, but rather to consider the rules we each accept and how best to apply them. We each have a unique opportunity to contribute to improved standards for the ethics of research with human subjects, both nationally and internationally. It is not our intention to devise and adopt new international standards. We each of us speak in our own names and from our own perceptions and experience, not as the official voices of our respective governments or agencies. Our goal this week is to clarify pressing issues and to formulate recommendations for policy makers of each of our countries to consider. These may be with respect to the refinement and expansion of the underlying principles themselves or with respect to the interpretation and implementation of these principles into practice.

Practice is at the core of the ethics of research with human subjects. As the background paper delineates, agreement about fundamental principles after all does not take one very far. It does not determine which principle takes priority when two come into conflict or how best to ensure that the principles are followed. I believe that it is in this area that we can make the greatest contribution towards improved standards. Understanding of the process, of the practice and of the specific mechanisms to translate the underlying principles of ethics review into action is what we seek to improve. Such translation is never simple. The difficulty in protecting the autonomy and confidentiality of the subject in AIDS research and at the same time encouraging the advances necessary to safeguard society clearly illustrate for us all the complexity of the decisions. Our discussion of the issues involved can perhaps

help our countries and agencies to form ground rules for dealing with this and other urgent problems that face society and the world today.

Our primary purpose then in my view is to better our national practices, and should it prove desirable and possible, to contribute to improved international standards as well. The degree to which national traditions can be transposed to another social context is of course a key question and one that is a part of our agenda.

The need for a broad synthetic and international perspective on the human context of research with human subjects is becoming increasingly evident. Ours is a world with shrinking boundaries, an international society where we work together as a global community and no longer function as isolated communities which may reasonably embrace quite different standards. The more one is privileged to work in the area of the ethics of research, the more one is convinced that the problems posed in this domain are ones which transcend national borders and which must be discussed and resolved in an international context.

At this point I would like briefly to review the conference agenda, which is mapped out in detail in the background paper for the conference. Overall the program is organized into four sections. Section I deals with the Principles for Ethics Review of Research with Human Subjects. This includes both the philosophical concepts and the practical principles involved in risk/benefit evaluation and the management of research.

Section II concerns Development and Implementation of National Ethics Standards. Each country has developed standards in its own cultural and institutional context. Understanding of the processes employed in one country may contribute positively to the development of better standards in another. We shall discuss the role of research institutions, the government, industry and the public in the ethics review process, the scope of coverage of standards and the methods used to apply them. We shall also address the accountability of the ethics review process.

The third section of the agenda treats Special Topics in Biomedical Ethics. These problematic areas of research include among others research with those with restricted ability to give consent, like children and patients with Alzheimer's disease, the controversial issue of research with embryos and ethics issues raised by industrial research. Within this section we shall approach the international context with consideration and experience of other countries and agencies. If there are additional points of special importance to you which are not covered in the agenda, may I encourage you to raise them in the discussion or in your presentations and comments?

It is my hope that we shall learn from our reexamination of the principles and practices for ethics review. I do not think practices have been looked at to a sufficient extent. Sharing our experiences and our current issues of concern may enable us to move beyond general principles to a definition of necessary minimal concrete procedures for their implementation towards improved standards for the ethics of research with human subjects.

Prime Minister Nakasone of Japan and Chancellor Helmut Kohl of the Federal Republic of Germany sent greetings.

Dear Prime Minister,

Please accept my heartfelt congratulations on the opening in Ottawa of the International Summit Conference on Bioethics.

As a convinced advocate of these Conferences, which have been held successfully each year since 1984, when the Conference on Life Sciences and Mankind was held in Tokyo, I find the valuable exchange of opinions on various important themes that has taken place in them most enlightening and encouraging.

It has become increasingly clear in the course of these discussions that the rapid advances in the life sciences being made today will both open up great possibilities for mankind and present human beings with difficult ethical and philosophical questions that human society has never before encountered. Humanity must strive in every way possible to resolve these problems, in the interest of human happiness and further progress in the life sciences.

The most important principle to remember when confronting these problems is that human life is the most precious thing nature gives to each human being. It is for this reason that these questions must be approached not only as the concerns of the specialized areas of the natural sciences but also interdisciplinarily and in the very broadest perspective, one that includes the social sciences, the humanities and also the sciences of religion. We must, at the same time, make every effort to ensure that the results of such study shall be shared not only by specialists but also by the general public as a whole.

In the Orient, we have the ancient saying "Medical sciences is love (jin)." "Jin" is, of course, the supreme moral value. I believe that only when we see this saying as extending to the life sciences as a whole will their sound development be assured.

The theme of the fourth conference is "Towards an International Ethic for Research with Human Beings." I shall be most happy if in their discussions the Conference participants, agreeing with me, approach the various issues from the broadest possible perspective.

I am convinced that the three participants from Japan, Professor Shigeaki Hinohara, Mr. Eiji Suzuki and Professor Koichi Bai, who are among Japan's leading authorities on these questions, will make a very significant contribution to the Conference.

I look forward to hearing from you, Mr. Prime Minister, of the Conference's achievements when we meet in June at the Summit Meeting in Italy.

Let me express, also, my most sincere thanks to you and all in Canada who have done so much to ensure the success of the Conference.

Yasuhiro Nakasone
Prime Minister of Japan

Greetings from the Federal German Chancellor
on the occasion of the
Conference "Towards an International Ethic for
Research with Human Beings"
Ottawa, April 1987

After the meetings held in Hakone, Rambouillet and Jakobsberg, this is the fourth time that eminent scientists from the Economic Summit Countries have gathered together to discuss ethics problems relating to the field of scientific research.

Last year's conference in Jakobsberg dealt with the ethical problems encountered in the field of neuroscientific research. Now in Ottawa, participants will be discussing ethical problems as they relate to the entire field of research on human beings.

The development of medical science has always simultaneously generated questions of ethics. The rapid advances made in the fields of medicine and biology and the progress achieved in unravelling the secrets of nature have opened up opportunities for doctors and medical researchers which were quite unthinkable just a few years ago. But at the same time, a doctor who also practises research is faced with a growing dilemma. His duty to care for his patients and his responsibility to respect the dignity of the individual are in conflict with his desire as a researcher to gain new knowledge which could benefit many people in the future.

In view of the rapid progress which has been made in the natural sciences, it has become increasingly difficult to draw the delicate line between therapy and unacceptable experimentation. Therefore, doctors and scientists who are carrying out research for and on human beings must develop ethical criteria on which to base their decisions, drawing on their vast knowledge and ever mindful of the awesome responsibility which they bear. Even in borderline situations they must guard the dignity of man, protect the life of the individual and show respect for Creation.

If the discussions to be held in the coming days produce results which will help practising doctors, scientists and politicians alike to live up to their respective responsibilities in this field, then a great deal will have been achieved for the well-being of mankind and the progress of medical science.

With these thoughts in mind, I wish the Conference and its participants every success.

Sincerely,
Helmut Kohl

Background Paper

Towards an International Ethic for Research with Human Beings

by Judith Miller

I. Introduction

1. Public Policy for Biomedical Ethics

In April 1987 Canada hosted the fourth of the Summit Ethics Conferences. The first conference, held in Hakone, Japan in 1984, debated general social, legal and ethical questions arising from recent developments in the biosciences. The second meeting in Rambouillet, France in 1985 focussed on modern genetics and the capacity for new reproductive interventions. In 1986 in the Federal Republic of Germany, delegates probed the important ethical and legal issues arising in the neurosciences and neuromedicine. The 1987 meeting focussed on a priority area in biomedical ethics that affects many research disciplines, namely the process of the ethics review of research with human beings.

Ethics are principles of right conduct, guiding what ought to be done. Ethics are not static but evolve with time and public perception.

Early advances in medicine were largely based upon anecdotal observation of the effects of various treatments. These treatments were applied largely at the discretion of the physicians who were guided by their own ethics and by principles such as those of the Hippocratic Oath. Although that oath does not explicitly consider medical research, the responsibilities assumed by physicians towards their patients can be extrapolated to an ethical responsibility of physicians or investigators towards their research subjects.

It is mainly in the last half century that standards for the correct treatment of subjects of research have moved from the hands of the individual physician towards a more public stance. International and national codes of ethics have replaced the original position of "laissez faire". Such codes outline particular considerations raising ethical dimensions in the research context about which investigators ought to be aware and responsible, they support the belief that science can function only within the limits set by the broader society. They delineate the principles that must be taken into account in order to balance the many different concerns of different members of society: the conflict between individual rights and social needs; the distribution of risks among different sectors of the population; and the freedom of scientific inquiry with its expected generation of new knowledge.

With respect to human subjects, the codes rest on a fundamental respect for the freedom and dignity of the individual. They attribute primary importance to the principle of autonomy and its practical implementation in informed, voluntary consent. The researcher has ultimate responsibility for conduct of research according to these principles.

2. History of International Codes of Research Ethics

Essential ethical principles have been affirmed in a series of international agreements: The Nuremberg Code established in 1947, the Helsinki Declaration, adopted by the World Medical Association in 1964 and modified by this Assembly in Tokyo, Japan, in 1975, and again in Venice, Italy, in 1983, and the Proposed International Guidelines for Biomedical Research Involving Human Subjects endorsed by the World Health Organization and the Council for International Organizations of Medical Sciences in 1981.

Stressing the values of human freedom and the sanctity of human life, the Nuremberg Code specifies what the relationship should be between experimenter and experimental subject. It stresses the welfare of the subject as of basic importance to the investigator regardless of the objectives of the planned research.

The Declaration of Helsinki/Tokyo set out more detailed rules to guide "biomedical research involving human subjects". Some important new requirements were: review of protocols by an independent committee, a statement of ethical considerations in a protocol, nonpublication of research which violated the principles laid out in the Declaration, and a distinction between consent requirements in therapeutic versus non-therapeutic clinical research.

The Proposed International Guidelines extended the principles of the Helsinki/Tokyo Document to the situations encountered in developing countries. The Guidelines took into account socio-economic circumstances, national legal provisions and administrative arrangements, as well as the special circumstances raised by external sponsorship of research. They emphasized the very important role of prospective examination of research by an independent committee which would appraise the protocol on scientific and ethical grounds. This is especially critical in view of the many cases where research may be desirable, even with subjects unable to give informed consent. These cases range from the need for research with children and the mentally ill to the need for community based research to assess and monitor accepted interventionist public health policies. In all of these, the informed consent procedure is seen as an insufficient means by itself to protect the human rights and welfare of research subjects.

3. Principles and Practices

Respect for persons (autonomy), not harming others (nonmaleficence), benefiting others (beneficence), maximizing benefit (utility) and justice are basic principles which apply to decisions in medicine and health care. These give rise to secondary principles such as truthfulness and rules such as the giving of informed consent, the weighing of potential harms and benefits of research and the equitable selection of subjects for research.

The translation into practice of principles to guide research with human subjects is not easy. Even with agreement about fundamental principles, it is unclear which principle takes priority when two come into conflict or how best to ensure that the principles are followed. What criteria are to be applied by whom and with what controls? Furthermore, the general principles espoused in international documents have different connotations in different cultures and countries and at different times. Each culture will apply the term "respect for persons" to its own version of the good and the just. National perspectives on individual freedoms in Eastern block, western and developing countries, for example, will colour the interpretation and application of ethical principles for research.

Individual nations have developed their own principles and procedures of application for ethics review. In general these are in keeping with the broad principles adopted internationally. Advances in science and technology and changes in ethical sensitivities of those involved make the application of general principles to particular cases an evolving art. In recent years, studies of research ethics have been conducted in many nations.

At this time it is desirable to come together to examine the variety of experiences in resolving the difficult dilemmas of ethics review in the health sciences research. New principles may be needed or old principles modified to respond to changing situations. Joint consideration of the responsibilities of the investigator, the research institution, the research funding agencies, the public and governments may be constructive. Reflection on the processes of development and operational implementation of ethics review used in one country can contribute to the development in another, and lead to improved international ethics standards.

II. *Development and Implementation of National Ethics Standards*

1. Development of National Ethics Standards

Each nation has developed its own standards for ethics review. These may give predominance to one principle over another or may add new concepts such as "fairness" to those accepted internationally. The standards may be defined in detail and set in firm centralized regulations with clear sanctions, or they may be left more flexible as guidelines subject to local interpretation. The latter are seen by some as more appropriate to deal with the numerous political, social, religious and ethical parameters intrinsic in research with human beings and more amenable to the progress of science. Through interpretation of guidelines, a local committee can weigh the many factors intrinsic in ethics review of research, e.g.: the scientific validity of a protocol, the necessity of prior animal experimentation, the differentiation of patients and healthy volunteers, the problem of consent, and the potential individual and social harms and benefits. It is hard to frame manageable legislation to balance such elements of ethics review.

Whether based in guidelines or in law, the scope of standards may apply only to limited areas such as drug research or research supported by government grants or they may apply broadly to protect subjects of all research in a country. Compliance with ethics guidelines may be voluntary or compulsory. Different sets of standards may be in force for university researchers and for industrial laboratories

seeking to market a product. Distinctions may be made between so-called therapeutic and so-called non-therapeutic research.

The method of arriving at standards vary. The research community, the medical community, governments and the public participate to greater or lesser degrees. Given the primary emphasis on respect for persons and the many subjective judgements in the choice and application of the principles, the role of the public is important. This role differs from country to country. The participating public is defined in different ways and invited to participate in different capacities. In some cases, standards emerge on a consensual basis with public input an integral part of the original development of standards, part of the process of ethical review of research and part of the monitoring process. In other instances, there are more limited opportunities for public input, perhaps in the mode of an appeal process or by participation of selected, well defined groups or individuals. In other countries, government officials serve as representatives of the public and the development and implementation of ethics standards occur through a more bureaucratic approach. The extent, timing and definition of public participation help shape the system of ethics review.

Understanding the process of development of ethics standards in different nations is a valuable step towards improved ethics standards. Several fundamental questions for development of national ethics standards for research with human subjects are:

- How and for what are standards set?
- What is the role of governments, the research community, funding agencies and industry in the development of standards?
- What are the advantages and disadvantages of alternate approaches such as legislation or guidelines?
- What is the role of the public in formulation of standards?
- Who speaks for the public?
- What is the relationship between international standards and national approaches?

2. Implementation of National Ethics Standards for Research with Human Subjects

Operational procedures are at the heart of the ethics of research with human subjects. In implementation, the principles are interpreted in the context of local conditions and institutional structures which define the role of researcher, industry, research institution, government and the like. Thus, for example, it may be reasonable to require a physician to be a member of an ethics review committee in an industrialized country with one physician per 1000 inhabitants, but untenable in a developing country where there may be only one physician for sixty thousand inhabitants.

An independent review committee has become the generally accepted mechanism for ethics review of research. The composition and procedures of such committees may be precisely defined or somewhat vague. Variation in the membership may influence how the committees function. Increasingly, community members have been included on review committees, rather than only specialists.

The research ethics review committees tend to have responsibility to examine the assessment of potential harms and benefits, the informed consent of subjects and the competence of the investigator. Review of scientific merit by research ethics review committees is a controversial subject; some address it, others do not. Value decisions are made on a case-by-case consideration of research protocols. The scope of review varies. It may include pilot studies, novel therapies, behavioural research or limit itself to a narrower definition of biomedical research.

In most cases, review committees have been established at an institutional level, i.e. where the research is to be conducted, or on a regional basis. This facilitates local variation and input but works against uniformity across a country. In other countries, review is centralized through professional bodies such as a National Academy of Science or a Ministry of Health or internationally within a body such as the World Health Organization. Responsibility is often divided between centralized governmental agencies and local institutional committees.

Several questions are of continuing concern in the accountability of the ethics review process. Key points for discussion are: the means for ongoing review and monitoring, the degree of compliance achieved and by whom, and the controls and sanctions available and utilized should departures from ethics standards occur.

III. *Special Topics in Biomedical Ethics*

Some research raises special concerns, because of methodology, purpose or subject matter. Several problematic areas are identified. These will be dealt with in a series of workshop sessions.

1. Research with Those with Restricted Ability to Give Consent

It is generally acknowledged that, wherever possible, research should be done with adults able to give free and informed consent. Research with vulnerable subjects with restricted ability to give consent poses special ethics problems. This includes research with children, with the infirm and with those in potentially coercive circumstances such as prisoners.

However, in some instances results of research undertaken in competent adults can not be extrapolated to the vulnerable population. If research is to be done on such topics as sudden infant death, appropriate pediatric drug dosages, and Alzheimer's disease, then members of vulnerable populations must apparently serve as subjects.

Despite the ethical difficulties intrinsic in the participation in research of such subjects, it can be seen as equally objectionable that research into such conditions should cease.

Key questions for discussion are:

- Under what conditions is research with those with restricted ability to give consent to be permitted?
- Is the criterion of minimal risk a workable concept for research with such subjects?
- Who acts on behalf of these subjects?
- What role, if any, is there for assent, in so far as the potential subject can understand the proposed research?
- How does one weigh the limited potential benefits envisioned for the individual versus those for society?
- What criteria should/do guide ethics of experimentation with the terminally ill?

2. Research with Embryos and Fetuses

Fetal and embryo research raises special ethical questions. These have come to the fore with the emergence of new capabilities in genetic manipulation and in reproductive technologies. Many groups have worked towards guidelines, often recommending that research be permissible with embryos up to 14 - 17 days of age. Consideration of the current practice and problems encountered with respect to research with fetuses and embryos may help delineate ways to apply accepted principles in these difficult areas.

Key questions for discussion are:

- What guidelines are currently in force or anticipated?
- Who administers them and for whom?
- What is the underlying rationale for positions taken and is it sound?
- How can one deal with the fine line between research and therapy in such areas as embryo research related to *in vitro* fertilization?
- How can public policy deal with the controversial ethical questions surrounding research with fetuses and embryos?

3. Ethics review of pilot studies and the introduction of novel therapies

Review procedures may not protect the subjects of pilot studies and of novel therapies. Sometimes pilot studies are excluded from review since they precede scientific trials and may not themselves lead to scientifically valid results. Novel therapies, interventions which are not part of traditional medical practice and not undertaken as formal research protocols, may also fall between established review systems.

Particular questions for discussion include:

- What is the distinction between research and therapy?
- What review mechanisms, if any, cover the areas at the interface between research and practice?
- What is the relationship between research ethics review and the doctor-patient relationship?
- What should be permitted and by what criteria in experimental use in critical situations of new drugs and devices which have not yet met regulatory requirements (compassionate exemption)?

4. Ethics Issues in Industrial Research

Industrial research raises a number of questions. Inducements to research personnel or to subjects, conflicts of interest, compensation to the subject for any harm incurred, and the ultimate ends of the research must all be considered. Confidentiality is also of special concern, both with respect to access by company officials of results concerning individual subjects and with respect to information about the substances to be tested which may bear on risks to the subject. Legal liability is also an issue in industrial research. Liability can have a negative influence on the pursuit of valuable research; research into vaccine production has suffered from this difficulty in some countries.

Key questions for discussion include:

- Do privately sponsored commercial studies require the same standards and guidelines as other research, or alternative or additional requirements?
- What conflicts of interest are likely to arise and how can one protect against them in industrial research?
- What special approaches may be necessary to protect confidentiality, both of subjects and of proprietary interests?
- What solutions (might) reduce the potential negative influence of legal liability?
- How effective are schemes such as "no-fault" insurance or government responsibility for research in areas of public need?

5. Ethics Standards for Research Across Nations and Cultures

Nations may have different principles and different procedures for dealing with the ethics review of research with human subjects. Even when different nations adhere to common international principles, the emphasis on particular principles, the understanding of the meaning of the principles and the translation of these principles into practice vary from country to country.

When research is done by a researcher from one country in another with different standards, the standards of the country where the research is being conducted must be respected. A dilemma arises when the standards where the research is being done are less rigorous than those of the researcher's own nation or of an external agency sponsoring the research. On the one hand it seems ethically unsound to provide fewer protections for inhabitants of another country than for one's own. On the other hand, it is equally problematic to adhere rigidly to one nation's standards and practices when they do not coincide with those in the country of the research subjects. Practices of one country may be impossible or unsuitable in a country which differs significantly with respect to such features as cultural and religious tradition, socio-economic pattern, demographic profile or health care and health sciences infrastructure.

Key questions for discussion are:

- With respect to the Economic Summit nations, how is cultural variation accommodated in the standards of research practices?
- How does this accommodation differ for standards that are used within the country and research that involves several nations?
- Does the experience with multinational studies inform us of difficulties encountered and the efficacy of methods used to address them?
- How might/do representatives from several cultures with somewhat different standards work together for the protection of research and of the research subjects?

6. Ethics of Choice of Research Topic

The choice of topics for research has ethical implications. Such choices are evident in decisions to support research concerning only some health needs. These decisions are made for a variety of reasons: the small populations affected, the lack of an adequate market to make the research "profitable", fear of excessive legal liability for the researchers and producer, or the weight of accepted medical practice.

Key questions for discussion are:

- What factors influence choice of research topic?
- What compensation for injury should there be for research subjects?
- On what basis and by what means might research be directed towards international needs?
- What problems and successes have been encountered in directed funding of research?
- What role, if any, should the Economic Summit nations play in such directed research?

IV. Towards Improved Standards

The Conference concludes with consideration of biomedical research ethics in an interdependent world. The other topics discussed, i.e.: the principles for ethics review of biomedical research with human subjects, the development of national ethics standards and practices to implement these principles, and problems and solutions in a variety of research areas of special concern, provide vital background for such exploration.

The need for standards at an international level is increasingly evident. Ours is a transnational society. Multinational companies conduct research in many countries. Collaborative research among nations is becoming more common. Such undertakings, as well as research within a given nation, would benefit from improved international ethics standards. It may be possible to enlarge and build in more detail upon the general principles for the conduct of research with human subjects established in international codes and accepted in many countries.

A key issue if such expansion is to be possible is the transferability of systems of ethics review despite national variations. Ethics standards reflect values and beliefs and therefore may differ from country to country or even community to community. Practices in place must fit within institutional structures and functions. Practices will likely differ, for example, where almost all research is conducted in government facilities and health care is provided to all by the government from a situation where most research is privately sponsored and health care an individual responsibility.

Refinement and expansion of transnational standards require answers to the following questions:

- Is there enough common ground to permit transfer from one nation to another?
- What elements of national practice are considered critical?
- Are these unique to the institutions and traditions of that nation?
- Might it be advisable and possible for the nations represented at the Conference to go beyond current general international guidelines for the ethics of biomedical research with human beings?
- What new standards and activities might be of use in identified problem areas?
- Would it be desirable to start an International Association of Bioethics for Research with Human Subjects?



Session Reports

During the conference, delegates prepared session reports, which presented the highlights of a session. These reports were discussed, modified and approved unanimously in plenary session. They served as the basis from which the Summary Report of the conference was distilled.

Session reports are provided to convey the flavour and direction of the dialogue. Reports of sessions C through G are presented as approved by the delegates. In view of the extremely short time available for the preparation of reports of sessions H and J, reports of these final sessions have been expanded subsequent to the meeting to reflect the discussion more fully. The Canadian delegation reviewed the revised reports.

The Conference dealt at some length with multidisciplinary committees whose responsibility it is to review the ethics of health science research projects, a key element in the ethics review process. Many different terms are used to describe these bodies. In Canada the 1987 MRC Guidelines identify them as "research ethics boards". In the United States they are known as Institutional Review Boards. The United Kingdom tends to refer to them as Ethical Committees. The names have been left as the delegates used them and approved them in the session reports. It should be understood that these terms in general describe a similar function. The specific composition and mode of functioning of such committees differ somewhat in different countries, and in some cases in different locations in the same country. As the conference was addressing the general need for and nature of such bodies, the various terms used are largely interchangeable.



I. Introduction

Session C

Underlying Principles for Biomedical Ethics Review of Research with Human Subjects.

The presentations offered four fundamental principles or approaches for bioethics. The first is that the progress of science is the predominant value. The second gives the interests of society as a whole a foremost importance. The third is procedural rather than philosophical. The fourth gives the highest value to the dignity and liberty of the individual. It recognises the diversity of opinions within society and suggests that this diversity may find a balanced expression through local, regional or national, widely representative bioethical committees.

The delegates acknowledged the methodological value of all these models and recognised the protection of the individual as the predominant interest. Society must defend the individual. For persons capable of consent, the concept of "autonomy" holds; this concept expresses the right of an individual to have the final word on choices which concern him, including experiments on himself. However, strict adherence to this principle would deny the possibility of experiments on persons who, for a number of reasons, are unable to exercise their own "autonomy". Many, but not all of the delegates thought that experiments should be permitted even on humans unable to exercise their "autonomy", under three conditions. The first is that, when individuals are unable to protect themselves and to express their own consent, their personal rights must be preserved, e.g., by proper proxy consent by mechanisms established by society. The second condition is that an ethics review process, reflecting societal standards and not relying just on the standards of the individual physician, oversee the research. The third condition is that the experiments in question should be aimed at improving the conditions of the individuals themselves or of the group to which they belong.

The reason for this approach is that, without research, the very conditions which make the individual incompetent (e.g., mental diseases) would be hard to study and treat, a further disadvantage to the individuals concerned as well as to their population groups. Reference was also made to the socially and geopolitically important problem of consent by persons who, because of inadequate education, are unable fully to comprehend the implication of the experiments to which they would be submitted.

The delegates affirmed the need for societal review of research proposals. Each decision cannot be defined by law, yet the procedures by which decisions are reached may well be legally defined. The delegates also affirmed the requirement that research ethics boards act to ensure a social set of standards over and above those which arise from the standards of the individual investigators. However, the law should give only very general outlines. The main function of ethics committees

should not be to make these individual decisions unnecessary, but to raise the moral sensitivity of researchers by paradigmatic discussions of important cases and to make transparent, by rational argument, the moral principles and possibly conflicting interests involved in such decisions.

The practical realities of applying the principles of ethics to experimentation on human subjects were discussed mainly in the context of controls by individual nations over the drugs used within their borders. Research on drugs is presently the major type of research involving human subjects. The need for each nation to assure the safety and efficacy of drugs is evident. However, considering the ever increasing interaction among nations and the world dimension of the pharmaceutical markets, some international coordination is needed to avoid the performance of the most risky experiments on populations which are less well protected.

Three groups in society can be identified as carrying risks and benefits. The researchers or clinicians who carry out the trials and other research on the drugs carry the primary burdens of ethical responsibility for the research subjects. Their risks and benefits are related to their own conscience and reputation. The human beings on whom the research is performed carry the direct risks of research, though history shows that these risks are not great, on average; conversely, research subjects can gain the benefits of the high standards of care associated with good research. Society or mankind as a whole is the ultimate beneficiary from research through improved health standards, and suffers the risks of not ensuring that the research is carried out with the highest ethical concerns. When they develop and test new drugs, industrial concerns share these ethical burdens.

In all stages, including the very important stage of monitoring, the essential role of quantification of risks was seen as the most important control function of society, but one very difficult to achieve. This is carried out through local institutional review boards, guided by national and international guidelines. In recognition of the need for international standards, the delegates identified a need for the present Helsinki agreement to be reviewed and kept current.

II. Development and Implementation of National Ethics Standards

Session D

Development of National Ethics Standards for Research with Human Subjects

There was general agreement that health (medical) research should be guided by ethical principles based upon historical evolution of national, cultural and social systems as well as international guidelines such as the Nuremberg Code, the Helsinki Declaration and its various amendments and those published by the Council for International Organizations of Medical Sciences. However, international guidelines have, as yet, not been widely accepted since national ethics principles, policies and procedures are still evolving in most countries.

Rapid progress in bioscience has created an urgent need for national standards, and the growing interdependence of research involving human subjects among nations has created a need for international institutions and agreements in the elaboration of ethical standards for the protection of human participants in health research.

Ethical standards are primarily intended to protect research subjects at risk. These include vulnerable groups such as children, prisoners, pregnant women, the mentally incompetent and peoples of emerging nations. Investigators and manufacturers of new therapeutic agents may also be at risk and in need of appropriate protection. The promulgation and implementation of widely accepted ethical standards are necessary to provide justification for the conduct of research and thus promote progress for the welfare of societies throughout the world.

As national standards are established, consideration must be given to evolving international guidelines for research involving human subjects. These will permit research between nations and amongst groups of nations using common protocols, stimulate sharing of research results amongst nations and avoid unnecessary duplication and multiplication of research efforts.

The question of how common standards can best be developed and implemented considering the present diversity and complexity of the biomedical research enterprise occupied much of the discussion.

Several broad conclusions seemed evident.

1. Most industrialized nations have some kind of system or mechanism for setting standards and such a mechanism or system is often lacking in the emerging nations of the world even though they constitute almost 80% of the world's population.

2. Systems for the protection of human subjects tend to fall into two broad categories: (a) those imposed by law, and (b) those sustained by professional and public groups. The fact is that many nations have systems that combine both laws and professional traditions. These traditions function against a background of statutes and judicial decisions that constitute normative standards.

Despite these common themes, many examples were cited which demonstrate wide variations in both theoretical and practical interpretations of international norms.

In some industrialized countries, the creation of a process for protecting human subjects followed a centralized direction. Within the context of widely accepted codes, the addressing of specific problems and issues has tended to follow a wide variety of patterns not only between nations but even from one research site to another within the same nation.

The testing of drugs, the standards for acceptable data, the acceptance of data from one jurisdiction by another, the avoidance of unnecessary redundancy in the testing of drugs, the pros and cons of generic drugs, the relative effectiveness of legal, professional, educational and moral sanctions and the best way to protect vulnerable individuals, groups and nations all seemed to be matters on which complete agreement or perhaps even broad consensus has yet to be reached. These differences constitute a part of the reason why it is difficult to assure implementation of international norms or even to measure the degree to which these norms are applied in many parts of the world.

Finally, there was extended discussion of the fact that the public plays a critical role in ethical decision-making in democratic and pluralistic societies, not only as a beneficiary of research but also as a participant and as a potential victim of research.

The importance of public participation is recognised by the inclusion of lay members in multidisciplinary committees at every level. Such membership brings with it the obligation to provide education and to be educated in bioethics and ethical analysis. Polarization of debate as well as litigious approaches can be avoided through enlightened public participation.

The public, however, can also be a victim of research. This is the case not only when research is poorly designed or conducted in a faulty manner, but particularly so where research is not carried out due to certain moral positions or because it is not commercially profitable. While non-research reduces risks to certain vulnerable groups or peoples, including incompetent or less-educated subjects, non-research can also be harmful to those groups since it deprives them of potential benefits.

In conclusion, the public needs additional skills to participate fully in policy-making and to provide service on ethics committees. An enlightened public is a strong antidote to the imposition of professional norms that are narrowly self-regulatory. The multidisciplinary character of ethics committees provides for public accountability and credibility. Statutory limits can serve as a necessary framework, but the professional retains final responsibility in interactions with research subjects. Statutory,

regulatory and policy limits constitute norms that are developed through public debate and consensus.

Session E

Procedures to Implement National Standards for Research with Human Subjects

The first part of the morning was devoted to an introduction of different national systems in place for the ethical review of proposals for research involving human subjects. The presentations made it obvious that among the Summit Countries various approaches have been chosen. Thus, the system in the United Kingdom relies heavily on guidelines issued by the professions or governmental medical authorities; it was subsequent to such guidelines that Ethical Committees (ECs) were set up for each district. The functioning of the ECs is not governed by any legislation nor is it subject to review by any supervisory body or a national centre. The Canadian system is more informal, resembling in many respects the British one. In Canada, however, the Medical Research Council – rather than the profession – has taken a lead role in formulating ethical guidelines.

In the United States, the ethical review of research projects is governed by flexible regulations implementing general legislation. Each institution applying for government funds is required by law to provide appropriate assurances including the guiding principles, procedures and composition of its Institutional Review Board. The protection of subjects who are particularly vulnerable (children, pregnant women, mentally disadvantaged individuals, prisoners, etc.) is the subject of special regulations. In addition, legislation regulates the ethical review of non-government funded research relating to drugs, medical devices, biologics and food additives.

In Japan, at present over 65% of medical schools have their own EC; in a short time, committees will be functioning in all such schools.

In France, a National Committee was set up under a decree dated February 23, 1983. This body is made up of 36 members drawn from different scientific disciplines and various schools of thought, as well as doctors, lawyers, philosophers and parliamentarians. The Committee has issued a number of general opinions and has also given its views on some more specific issues. In addition, some hospital committees and regional committees have been set up in various parts of the country.

In the Federal Republic of Germany ethics commissions are nearly all established at the medical faculties of the universities. A conference of the chairmen of all university committees meets once or twice a year in order to compare the process of decision-making in the local committees. Others are installed with the regional Chambers for Physicians (Landesaerztekammer). There is a central commission with the Bundesaerztekammer, which is the organisation of all German doctors. Its function is to advise several medical and governmental institutions and to give guidelines in certain areas, such as *in vitro* fertilization and embryo transfer. The German Re-

search Foundation will only support research projects which have been reviewed and approved by an ethic committee.

Only a small number of Italian institutions have established their own EC.

The question of accountability of ECs was also raised, particularly in connection with research in reproductive and genetic engineering. Basically, the concern is still for the protection of the integrity and dignity of the subjects of research. These scientific advances, however, raise a whole set of new and very difficult questions, e.g. At what point of development does a new life entitled to human rights begin? How can one ascertain when death has occurred?

The second part of the session focussed on various aspects of local ECs, and in particular on:

- their composition
- their mandate or functions
- the nature of their conclusions
- their creation

I. *Composition*

There was general agreement that ECs should comprise not only experts in the field of the research at hand, but other members as well.

Several delegates intervened on the role ethicists should be playing in these bodies. In the United States, ethicists are found to participate well on ECs where their function is twofold: (1) to describe the moral values of the community, and (2) to analyse the ethical issues. However, it is not for ethicists to dictate what is right or wrong, that is, to assume a normative function. In France, the National Bioethics Committee has among its members representatives of five "spiritual and philosophical families".

It was also questioned whether lawyers should automatically be appointed to ECs. Some feared that in certain instances lawyers could find themselves in a conflict of interest situation. Thus, lawyers of research or funding institutions might be more concerned with protecting their institution than with safeguarding the interests of the subjects of research. It was felt - perhaps unduly - that lawyers were often inclined to equate what was moral with what was legal. Others, however, found that legally trained professionals (for example, magistrates and law professors) could make a valuable contribution to the work of ECs.

Finally, it was agreed that the composition of ECs should vary according to whether an EC was simply advisory or had decision-making powers or whether it was attached to a hospital or, for instance, a pharmaceutical industry.

II. *Mandate and Functions*

The point was made that an EC should be concerned with research as opposed to the practice of medicine ("deontology"), a matter which should be left to the profession to regulate.

When should an EC review innovative procedures? It was pointed out that it was not always easy to distinguish among general practice research and innovative procedure. So long as the latter is concerned with the well-being of the patient, then, it should not be a matter for EC review. If, however, the procedure is conducted for the purpose of acquiring new knowledge, then it should be referred to an EC. In the final analysis, it is up to the physicians to act responsibly.

What should be the role of ECs regarding the monitoring of research projects they approve? In the United States, the law provides for a system of "continuing review" according to which the researcher must submit a report to the EC on an annual basis or more often if so required. The report deals with the progress achieved, any change in the research methodology, adverse reactions, etc. However, the ECs do not have a monitoring function as such.

Finally, reference was made to the "educational" function of ECs, even towards their own members.

III. *Nature of EC Conclusions*

At issue here was whether ECs should be advisory in nature or empowered to make binding decisions. However, much of the discussion centred on what appeal mechanisms were available to a researcher whose project had been turned down. In most instances, the researcher will agree to modify the protocol to satisfy the ECs concerns. In the United Kingdom, if differences between the EC and the researcher are irreconcilable, then recourse is had to an outside arbitrator chosen by mutual agreement or, failing that, by the professional body concerned.

In the United States, where a disagreement persists between an EC and the authors of a research proposal, a second EC is constituted which listens to the matter "de novo" and arrives at a final decision. Recourse to this mechanism has been used only in ten instances in the last seven years.

IV. *Creation of ECs*

Little time was left for this topic. The question was asked, however, whether, in addition to local ECs which have primary responsibility for the review of research protocols, there should not be created a National Committee – such as that created in France – with a mandate to issue guidelines ("des avis") on topical ethical issues.



III. Special Topics in Biomedical Ethics

Session F

Issues Related to Consent

Research with the Incompetent

The discussions on issues related to consent reflected the widely different views and concerns which have occupied people in many countries. In considering research with those with restricted ability to consent, the delegates focussed on research with children; some discussion on research with prisoners and the mentally incompetent also took place.

The central concern about research with children is a dilemma. On the one hand is the need for research; on the other is the need for consent by individual subjects of research as the means of protection of their individual rights. Consent is a basic ethics requirement of research, yet children cannot give fully informed consent. If research which may cause harm is to be done, alternate means of protecting the individual child must be found.

The delegates reaffirmed the statement in the report of Session C that research with children is necessary if treatment of childhood disease is to advance. There was agreement that the needed research can be justified *only*: when the specific project is permitted by an ethics review process which reflects societal standards; when all needed knowledge has been obtained through research with adults or animals; when there is no valid alternative to the use of the children in the research; when a valid proxy consent (by family, guardians, ombudsman, those with power of attorney or others) has been obtained for each research subject; and when, to the extent possible, the child has given assent.

The discussions centred on two details implicit in these requirements. The first was the philosophical framework within which the proxy consent is given. The second concerned the relationship between the extent of risks which can be envisaged to the child and the improvement to the health of the child which is expected as a result of the research.

Three philosophical frameworks were presented, "best interest of the child", "substituted judgement", and "balancing of interests".

The "best interest of the child" permits only those choices which are judged to benefit the child. It does not express autonomy, because the child does not consent for him or herself, and because it does not include the option of deciding against one's own best interests. "Substituted judgement" calls for a judgement of how the incompetent subject would have acted were he or she competent. This judgement may

be well founded for a person who once was competent, but for an infant there can be little guidance. The possibility that "substituted judgement" might enhance the autonomy of the individual was suggested, but not supported since the reasonableness of such a decision can be second guessed.

The "balancing of interests" framework explicitly denies the impression that proxy consent preserves autonomy; instead, it shows that the judgement to be made must balance the interests of the individual child and the interests of other children in similar situations in the future.

This "balancing of interests" standard is most acute when the proposed research envisages no direct health benefit to its subjects, but is carried out because of its potential benefit to other children in the same situation. Some delegates advanced the view that children should not participate in research which is not of direct benefit to them. Others, however, did not agree with this absolute prescription. A number of reasons were advanced. Should research with minimal risk be allowed, for example, the study of patient records, or sampling urine or blood? Also, to what extent would this prohibition deny research into certain diseases of childhood? Also, would such an absolute interdiction encourage attempts at evasion by trying to incorporate an aspect of therapeutic benefit into an otherwise non-beneficial research program? If the prohibition is softened to allow non-therapeutic research of minimal risk, how is "minimal risk" to be defined? One country refers to risks comparable to those which parents would accept for their children in the normal course of their lives, for example in sports, travel or school. However such risks are taken voluntarily by parents on behalf of their children and their quantification as comparable to research risks is problematic.

The discussion also considered the above concerns in the context of different groups of children, those who are healthy, acutely or chronically ill, or dying. A strongly expressed view was that a child who is dying should not be a subject of research when it might merely delay the moment of death. This view was again contested, since such research might be the only way to achieve essential knowledge. The detailed processes of ethics review as well as proxy consent should be relied upon to preserve societal standards.

The delegates also briefly discussed research conducted with people in prison and with the mentally ill. The ethical acceptability of allowing prisoners to participate in research again raises a dilemma between the obvious coercions possible in obtaining consent, and the denial of autonomy implicit in preventing their volunteering as subjects. This dilemma was not resolved, and discussion ended when it became clear that only very few industrialized countries permitted research involving prisoners.

The brief discussion of research involving the mentally ill raised concerns that were similar to those with children.

Embryo Research

The integrity and uniqueness of human life in its earliest embryonic stages of formation are generally recognized by agreement on the need for regulation of research on human embryos. Current forms of control of research procedures and manipulation of human genetic material are not legislative in nature. In fact, in the almost total ab-

sence of legislation, research on the embryo is presently governed by the self-regulatory efforts of scientific and professional bodies, the centres themselves, and by review by ethics committees, local and national. Voluntary licensing control exists, for example as in England, but there was consensus on the need to regulate the current anarchic proliferation and operation of *in vitro* fertilization centres in some countries while acquiring the workable experience necessary for effective legislation.

Internationally, certain common prohibitions on the more extreme uses of research (creation of chimeras or hybrids, cloning of embryos, genetic modifications in the germ line, commercialization and unspecified long term storage) as well as a 14 day limit on *in vitro* growth, are emerging in the recommendations of government commissions and in the reports of professional bodies. Some countries have also recommended prohibiting the implantation of embryos that have been the object of research. While most reports did not recommend the granting of legal personality to the early embryo *in vitro*, there was a general recognition of the value of this human life, of its human potential and completeness. Legal personality is not the issue then, but rather whether a newly formed human being is sufficiently worthy of protection that it should not be used, arbitrarily kept alive, or destroyed.

One position maintained that no distinctions should be made that are based on stages of embryonic development and thus human life should be protected from fertilization onwards. Such protection would preclude the deliberate creation of embryos solely for research purposes and prohibit the unnecessary destruction of embryos. Furthermore, surplus embryos could be used for research only if such use would make possible advanced medical knowledge not otherwise obtainable. The avoidance of any instrumentalization of human life, its possible reification and treatment as an object demands this high level of respect and limitations on possible uses in research.

Another position could be labelled as "principled pragmatism". It recognized the potentiality and preciousness of the embryo. Nevertheless, the need to improve treatment of infertility, the possibility of testing the fertilizing capacity of sperm and the limited supply of embryos were among the justifications for the use of embryos in research. Moreover, according to this position, the manipulation of human life through medical intervention and scientific study effects an economy of natural biological wastage, rather than an unnecessary assault on potential human life. It can be achieved only by allowing research on embryos. Genetic information that can be read in gametes and embryos, formed into scientific knowledge and put to use to benefit human kind, is thereby justified, but only on embryos up to 14 days. This 14 day limit corresponds to the embryonic organization, differentiation and individuality and is biologically and scientifically recognized.

Nevertheless, others would differ with the legal and philosophical reasoning of these two positions as well as with a distinction based on a 14 day limit. They hold a view of the ontological status of the fertilized ovum which gives it a moral status that precludes any embryo experimentation.

Several questions were raised with respect to the applicability of legal concepts of "ownership" (more properly discussed in terms of legitimate interest in), and control of, human genetic material during storage or after the death of donors. Questions also remain concerning penal sanctions as opposed to professional regulation and the

acceptability of research on embryos under certain conditions (informed consent of donors, ethics committee approval and in approved centres only).

There was common agreement on the immediate necessity of controlling and regulating centres and physicians currently engaged in *in vitro* procedures or research on human embryology. Considering the experimental nature of *in vitro* fertilization, its low success rate and the unknown long term effect of these procedures, which though "therapeutic" in nature for the infertile have implications for the manipulation and control of human life, work with embryos even as a treatment for infertility should be regarded as developmental procedures that are experimental in nature and therefore be closely monitored.

The delegates affirmed the need to balance the regard for the human interest in the embryo with professional liberty for clinical treatment and for scientific inquiry in the interest of progress in medical knowledge and skill. To this end they recommended the supervision of centres offering IVF and related treatments for infertility and conducting embryo research, with procedures regulated according to appropriate guidelines administered by a competent authority.

Session G

Areas of Special Concern

Ethics Review of Pilot Studies

Pilot or preliminary studies are an essential phase of a continuum of therapy and research. This continuum can be said to start from clinical observations; a possibly valuable observation may be tried out on other patients because the physician believes that the patient may benefit. If promising, but not definitive results are seen, formal research should be undertaken to test whether an advance has really been found. If the answer is positive, the innovation becomes incorporated into therapy.

The pilot studies reflect the phase between the initial observation on one or a few patients and the start of full-fledged, protocol-based research programs.

The decision on when the initial observations move from the domain of pure therapy to research ultimately depends on the integrity of the physician. The primary judgement is one of intent; is the desire primarily to help the patient, through the best possible therapy, or is there also a plan to determine whether the new idea has scientific value? As soon as the latter determination is recognized or possible, the researcher should seek the advice of the research ethics board, which should always be seen as a collegial source of societal advice and counsel rather than as an adversarial regulatory body.

Pilot or preliminary studies are just that; they help in formulating the precise questions which research can answer. They may even be required to determine whether or how a full research protocol should be done, for example on the grounds of whether the new idea does not seem to be much better than the existing one, or is ap-

plicable only to a sub-set of patients. Such preliminary studies then may make full studies unnecessary.

Because pilot or preliminary studies have the motive of adding to knowledge, whether or not there is also a therapeutic intent, the research ethics board must re-view the studies. The judgements to be made cover the same range of considerations as for more formal research protocols. They will tend, however, to focus on research which begins with observations on one or a very few patients. Close monitoring and scrutiny by the research ethics board is necessary before further steps or a larger protocol can be taken by the investigator.

With regards to other issues particular to pilot studies, a view was expressed that, if one research ethics board has agreed to a project whereas another has refused it, then patients whose consent is sought should be so informed. This idea was not supported since the reasons for refusal are not always explicit. Moreover, certain centres may refuse on ethical grounds, others for procedural or scientific motives. It was also agreed that differences of views between research ethics boards should be expected. Also, no research ethics board has absolute infallibility; human judgments are involved.

Two issues were seen to arise from these discussions, the exchange of information between research ethics boards and researchers, and the possibility of an appeal mechanism for researchers dissatisfied with the decision. It was agreed that there could be a far greater exchange of information on research ethics board decisions and on research directions generally. A centralized data base of information was not considered feasible, but a linked bulletin board or conferencing concept was discussed.

Finally, the delegates agreed that there should be provision for re-examination of a research project not approved by a research ethics board. This provision should be of a sort which would not encourage the overriding of local decisions by a higher or distant authority; but rather it should maintain the collaborative nature of the relationship between the researcher and the research ethics board rather than an adversarial relationship between them.

Industrial Research

With respect to the role of industries which are a major source of funding leading to medical innovation and the licensing of drugs or devices, it was noted that this research involves both animals and people and is often carried out by a certain industry in many countries. For that reason, the interactions between industries, governments and universities are of great concern.

Differences in ethics standards, and how they are interpreted and implemented can have direct economic effects which must be taken into account by industry, government and the universities. Failure to seek agreement can adversely affect mutual interests as well as the research subjects if others do not comply. Nations should therefore strive for common standards, and encourage adherence. For example, delegates agreed that no nation should allow or support research in other countries which is not at least equivalent to its own ethical review standards. However, the concern goes beyond such direct prescriptions. Nations should develop, in collaboration with national and multinational industries, international accords which strive for com-

mon attitudes and exchangeability of standards, as well as the development of mutual trust and respect for the roles of the different contributors to the development of health care.

Related to these needs for collaboration between sectors, and arising from them, was the request by delegates for incorporation into these discussions of the identification of emerging technologies so as to foster exchange on the new ethical concerns to be faced. Such interaction might help the equitable distribution of efforts in research and development in, for example, the treatment of "orphan diseases".

Delegates also discussed current ethical concerns raised by the economic drive of industrial research. The first refers to the growing pace of commercialization of products, and the increasingly close links between university and industry research interests. These raise the possibilities that academic researchers may have financial interests in the outcome of the research. The delegates believe that any such potential conflicts of interest should be declared to the research ethics board. Such conflicts result from the provision of equipment or the funding of meetings by the companies.

The second concern was stated but not resolved. The need for confidentiality of commercially sensitive material is evident; however, confidentiality cannot be consistent with the most complete review of the ethical aspects of the proposed research, and may actually lead to unnecessary repetitions of research when old data, of low commercial importance, are withheld. The delegates believe that this area should be the subject of further study.

A third concern arises from the ability to offer payment to research subjects. Payment can induce subjects to participate in the research, and favours participation by those of more limited means. Furthermore, subjects may then go to the research project which pays the most, thus leading to competition for research subjects.

Concern was also expressed over the need for compensation of patients for adverse effects arising from the research, but not from the underlying illness. Delegates expressed the view that means of compensation be instituted, but that, where this was not possible, the lack of provisions for compensation for injuries resulting from research be pointed out to potential subjects. Delegates distinguished two aspects of compensation, first, costs from injuries that may result and second, costs of participation in the research.

A final point concerned the need for commercial products to comply with national demands to meet safety standards. Often the precise tests are defined, for example, toxicity tests or tests of efficacy on animals. Some of these requirements which were generally appropriate when they were first promulgated, may now no longer be relevant. We encourage governmental agencies continuously to review their regulatory requirements to ensure that they do not demand test results of safety and toxicology which are no longer relevant or which can be replaced by satisfactory alternatives. The exchange of information should be encouraged to minimize the number of people put at risk.

The delegates affirmed that the same ethics review process should be used whatever the source of a new material. The delegates also stated that research ethics boards

and national standards for safety should require only information which has a substantive influence on the needed decisions.

Industrial research, particularly research required to meet national safety standards, also makes extensive use of animals in research programs. Delegates were of the opinion that appropriate and relevant animal research should continue to precede research with human subjects. However, ethical standards require the utmost care whenever animals are used in research, and effective *in vitro* tests are being developed to replace tests which use animals. The delegates urge national authorities to reflect these advances in their requirements.

Transcultural Ethics Standards

While there has been transcultural acceptance of ethics standards for research, these principled standards have resulted in difficulties when translated into procedures and legislation assuring their implementation in different nations and cultures. This is particularly so with regards to the monitoring and surveillance of drug testing where common standards between nations are rare. For these reasons, on a practical level, we need continuing debate and dialogue.

Furthermore, due to cultural differences, it was suggested that the practical implementation of transnational ethics be aided by the teaching of bioethics to the clinical investigators themselves. Such a mechanism should be formalized and be made part of the medical school curriculum. This goal of creating a common mode of communication on substantive ethics through the education of investigators on the ethical principles involved was generally accepted as a necessary first step towards a search for common procedures for implementation.

Session H

Ethics of Choice of Research Topic

Scientific, socio-cultural, ethical and economic realities influence the choice of research topics. From the scientific perspective, for example, the scientist will consider such aspects as the state of knowledge and research opportunities in the field, the significance of the knowledge sought, the credibility of the topic among scientific peers, the nature and difficulty of the research and of the likely field conditions. Ethical considerations at international, national and local levels, considerations which themselves depend on a variety of differing cultural, philosophical and economic factors, impose constraints on the choice of research topic. Other specific factors in the overall environment which influence research choices include: political and financial support for research on the topic, cultural or social sensitivities, the need for (special) human subjects or control groups, the potential for injury to the subjects of research as well as to researchers, matters of liability, and so forth. In addition researchers respond to humanitarian considerations, such as the wish to aid large or small groups of disease victims or the wish to find solutions for major public health problems and, in some instances, by the possible economic rewards which might ensue from successful research.

Individual researchers as well as research groups and institutions consider incentives and constraints when choosing research topics. Choices are made in the context of national policies and systems of support, as well as national policies and practices in respect to ethics. In some instances this results in an apparent imbalance between the research topics being chosen and major global needs for research in fields such as fertility regulation and some tropical diseases.

International research programs such as the World Health Organization's Special Programme for Research Development and Research Training in Human Reproduction provide a successful mechanism to promote and carry out research in those areas which are neglected, sensitive and/or economically unattractive to national researchers. These programs make extensive use of the international scientific community and apply high standards of scientific and ethical review in order to carry out research in areas of high global priority which are difficult to address on a national basis. The programs are in a unique position to acquire and use world wide comparative data derived from the scientific base of knowledge existing in both developed and developing countries. Indeed, the development of the programs is dependent on the existence of this basic knowledge which enables the programs to cover a broad spectrum of research, from the search for fundamental knowledge in the laboratory to the application of research results in the field.

The scientific and ethical review mechanisms established by such international research programs have been adopted by a number of countries as models for their own standards. The requirement for a local ethics review for a multinational project has led in several cases, for example, to review by the new ethics committee of all research in an institution.

The delegates agreed that research should focus upon the development of knowledge in broad fields of science with the aim of achieving a fundamental understanding of biological processes, even those which might not appear to have direct application over the short or longer term. Delegates saw basic and applied research as closely linked and interdependent. Spin-offs from curiosity driven basic research or research on a health condition which affects only a small number of individuals may have a potential application far beyond the immediate research. Large scale support for narrowly focussed, mission-oriented research on specific diseases without the necessary foundation of scientific knowledge was seen as rarely, if ever, successful. Recent research on AIDS, for example, would not have been possible without an understanding of the role of the enzyme reverse transcriptase in the pathogenesis of RNA containing viruses, research undertaken from scientific curiosity years before.

All research undertaken must be of high quality and must include the spectrum of studies required to facilitate the application of results as rapidly and as effectively as possible. In fact the failure to implement the results of research for the benefit of humanity has, in itself, serious ethical implications. Prevention of needless deaths and injuries through expanded immunization against infectious diseases such as measles is a case in point. The ethical weighing of harms and benefits by ethics review committees implies that the research benefits will be applied. That countries with the means should help support implementation of research results and should sponsor research in countries lacking such resources is an act of solidarity with these latter countries, a solidarity ethically required in present circumstances.

IV. Towards Improved Ethics Standards

Session J

Biomedical Research Ethics in an Interdependent World

The last decade has witnessed the search for improved communication and harmonization between nations, evident both in common endeavor and in international accords. Yet international agreements such as the valuable Helsinki Declaration tend to be very general in order to encourage universal acceptability while respecting cultural differences. Delegates supported both the feasibility and the need for further international development beyond general ethical principles towards the elaboration of international standards of practice of these principles for protection of human subjects of research. Certain ideas, while not transferable in their totality to all nations, contain elements that partially and progressively over time could form the groundwork for the elaboration of such an International Code of Ethics. One approach suggested was differentiation between a *minimal standard* to be universally applicable and *maximal hopes*, which would not be possible to realize on a universal basis but would provide ideals towards which to strive on a national level. The international discussion to refine standards would deepen and broaden mutual understanding of other cultures and help to develop consensus.

Delegates emphasized as well the need for nations to address together specific common areas of concern such as protection of vulnerable groups, community-based research and research on fetuses and embryos, all of which are treated only superficially if at all in existing international accords. Instruments in the form of commission reports or legal bills already exist on a national level. These instruments demonstrate the possibility of arriving at some consensus on difficult subjects (such as drug trials on human subjects, *in vitro* fertilization and brain death). While respect for cultural particularism is essential, it may be possible to derive common denominators from such national instruments in the search for commonality and universality.

The elaboration of an expanded International Code of Ethics could improve the protection of the dignity of human beings who serve as subjects of research, could foster a better understanding of ethics review in research on human beings on a national level and could avoid the exportation of research trials to countries with more permissive standards.

Delegates viewed the reaffirmation of basic principles and approaches as a way both to respect and protect the individual research subject and to make the human subject an *active* and educated participant. Delegates viewed participation of subjects in research intended to benefit human kind through scientific progress as a means for subjects to express basic human altruism and a desire to serve the common good in the spirit of solidarity.

The further refinement and expansion of national standards of research ethics with human subjects across political and cultural boundaries demands however a continuing investigation into the ethical problems in biomedical research. If the trivialization and bureaucratization of the research ethics boards themselves is to be avoided, it is recommended first that these committees, their operation, their function as well as the language used by such committees (moral philosophy, ethics, morality ...) be studied.

Delegates recommended intensification of education in medical ethics for physicians, investigators, medical students, research and hospital administrators, those involved in the review of research ethics, the media and the public generally. Patients are another key target for education as ethics is a matter of reciprocal obligation and patients need training too in ethical response in their relationships with doctors and researchers.

Delegates acknowledged that many effective educational materials and approaches have been developed, but are often inadequately circulated and internalized, particularly trans-nationally. It was thought important to find ways to reach the research community who often devote their educational time to specializing in their own fields rather than to broadening their understanding of biomedical ethics. One way to ensure that the practitioners are sensitive to bioethical principles and translate them into practice is to strive for the integration of ethics into clinical practice. Formal and informal medical ethics programs now exist in many of the world's countries. These programs should be used as a basis for instruction in this matter of integration, and for eventual achievement of it in all cases.

Finally, there was consensus that special attention should be given to the ethical issues involved in epidemiological and field studies which can be as intrusive on human dignity and privacy as physical intervention. This issue was seen as of great importance for international collaboration with respect to the serious problem of AIDS as well as in other fields. In particular, the laws governing confidentiality and protection of data, which both restrict the exchange and gathering of information and at the same time fail adequately to protect the subject of such epidemiological studies with respect to the communication of the information obtained, require examination. Attention should also be given to the question of any psychological risk involved for these subjects, particularly when ethnic populations are the focus of study.

In sum the delegates agreed on both the importance and the feasibility of improved standards through increased international collaboration on the ethics of biomedical research with human subjects. One common element thought extremely important was the establishment and maintenance of multidisciplinary research ethics review bodies. It may also be possible to articulate and agree upon other essential principles or desirable practices to implement accepted principles of research ethics. Delegates reached a consensus that key elements for improved standards include: continuing research on ethical issues related to human biomedical investigations, enhanced education of those involved in research and of the public more generally, and special attention to the ethics of epidemiological research. Delegates strongly endorsed further study and enhanced communication among countries as essential steps to improve research ethics.

Closing Session

Mr. Justice David Marshall: Dr. Law, Dr. Bois, Ladies and Gentlemen, good morning.

I would like to introduce Dr. Pierre Bois, President of the Medical Research Council of Canada, and Dr. Maureen Law, Deputy Minister of National Health and Welfare. We are very pleased they are able to be here today to receive the report from the Fourth International Summit Conference on Bioethics on behalf of the Prime Minister of Canada.

Coming from many countries and agencies and from many disciplines, we have worked intensively this week to share our insights towards a new ethic for research with human subjects. We have prepared a report which we hope will be useful to you and to other policy makers in formulating how you will contend with the difficult ethical and social issues intrinsic to research with human subjects.

Over the week we discussed many issues. We have grounded our discussion in consideration of the general principles which have been historically accepted in international guidelines. We have discussed at length the philosophy, the cultural context, and the methods used, in our countries and in our experience, to translate these general principles into practice. We have studied the development of national ethical standards and the procedures to implement national standards for research with human subjects. Areas of research receiving special attention were: issues related to consent, the ethics review of pilot studies and the introduction of novel therapies, ethical issues in industrial research and ethical standards for research across nations and cultures. We have brought our mutual understanding to bear on the ethics of choice of research topics and the effectiveness of directed research. These elements allowed us to build towards a consideration of the aspects of biomedical research ethics in an interdependent world.

Obviously the topic will require continuing consideration to meet demands imposed by the rapid progress in bioscience and the increasingly multinational character of the research endeavor. In our week of discussion, we have found areas of significant agreement and reached conclusions on steps which would improve, in our view, the ethics of research with human subjects.

(Mr. Justice Marshall reviewed the Summary Report and thanked all of those who contributed to the conference. He then presented copies of the report to Drs. Law and Bois).

Dr. Law: Mr. Justice Marshall, Dr. Bois and honoured delegates, ladies and gentlemen,

It has been a great pleasure for us in Canada to host this Fourth International Summit Conference on Bioethics. We have enjoyed meeting all of you and getting to know delegates from different countries, disciplines and backgrounds, an interesting

mix of medicine, law, science, religion, and philosophy. I am looking forward also to having the opportunity to read the final report of the conference in more detail. You are aware that our Prime Minister, Mr. Mulroney, will present this report at the Economic Summit in June.

The complexity of the topic and the short period of time which you have had to discuss and deliberate on these issues of great concern must have given rise to a certain amount of both exhilaration and frustration on the part of the group, exhilaration because you have had the opportunity to be in the company of experts from various interfacing and even overlapping fields and because the discussions were so wide ranging, stimulating and important. On the other hand, I am sure it has been somewhat frustrating because the complexity of the topics necessarily raises more questions than answers and the time that you have had available to resolve such weighty problems has not really been that long.

I am impressed that you have been able to draft this report, nevertheless, and to put forward advice and recommendations not only on specific issues, but also on development and implementation of guidelines for research involving human subjects.

In the area of ethics standards, the development of policies and procedures which deal with sensitive issues such as research involving children, human reproduction and industrial research is of great and continuing significance to all nations. I know that this report reflects a considerable amount of compromise as well as a great deal of agreement. That spirit of compromise is of critical importance in building international cooperation on standards for ethics research and in developing criteria which would lead to common protocols with and between countries.

As you have clearly outlined in your recommendations, these are standards which must always continue to protect those research subjects who are most vulnerable, such as children. So I would like to thank you now for the work you have done and to assure you that the efforts you have made are very much appreciated by the Government of Canada and I am sure also by the international community and will be of importance to people from all countries. Thank you very much.

Dr. Bois: Mr. Chairman, Deputy Minister, Distinguished Delegates, Members of the Press and the Public,

On behalf of the Medical Research Council of Canada allow me to extend my thanks and congratulations for the excellent work that you have accomplished. You have very successfully carried out a particularly arduous task that was assigned to you by the organizers of the Conference.

I am looking forward to a thorough study of your report and to reflection on the suggestions that you made to improve the ethics of research with human subjects. In our continuing work in this area, I am sure that the Medical Research Council of Canada will benefit greatly from your advice and recommendations.

These Summit meetings with representatives of a core group of industrial nations provide a unique forum for countries to come together to thrash out shared problems such as the ethical dilemmas in health science research.

I sincerely hope that your work and the report and the proceedings that will follow will enable Canada and the other nations represented here better to protect society, while at the same time ensuring the greatest possible freedom for scientific research from which we all derive so many benefits.

Finally, I would like to extend my thanks, not only to all the delegates but to the Organizing Committee, to the Conference Chairman, to the staff members of the Medical Research Council, of External Affairs and of Health and Welfare Canada and to the translators and interpreters who have made this event such a success. Tous mes remerciements.

Summary Report of the International Summit Conference on Bioethics

Towards an International Ethic for Research Involving Human Subjects

Ottawa, Canada - April 5 - 10, 1987

The Summary Report, based on discussion and recommendations considered throughout the Summit meeting, addresses major areas discussed throughout the week, presenting both the background and the major recommendations of the delegates. Delegates believed it important to consider the recommendations in context. Hence the recommendations are shown in boldface within the text.

1. Introduction

Rapid progress in bioscience has created an urgent need for continuing development of national standards of ethics in research with human subjects. The growing interdependence of nations throughout the world has stimulated a need for internationally agreed upon standards and practices based on a careful continuing dialogue and reflection on values. The delegates at the fourth International Summit Conference on Bioethics worked towards these goals. They focussed not only on the principles, but more specifically on the practice and procedures guaranteeing their implementation.

The fourth in a series of annual bioethics summit meetings initiated by Prime Minister Nakasone in 1984, this meeting reflected deeply on an area important to the entire practice of bioscience and medical research. It is hoped that the discussions and recommendations will benefit national practices, and contribute to improved international standards.

We, the delegates to this meeting, invite the Prime Minister of Canada, the Right Honourable Brian Mulroney, to present this report to the next Economic Summit Conference, to be held in Italy in June, 1987.

2. Underlying Principles and Practices: Development and Implementation of National Ethics Standards

The underlying principles for the ethics of research with human subjects are defined in national and international codes. These include respect for individuals, contribution to the well-being of peoples, and the equitable distribution of potential risks and benefits throughout society. Even though only very general international guidelines have been accepted, as yet, uniform practices are not widely accepted due to national and cultural differences.

Though need for societal review of research proposals is generally accepted, there are great differences in how countries and even institutions within some countries carry out this review. Only some of these variations can be ascribed to the cultural differences which are an essential background to societal standards.

As national standards are established, consideration must be given to evolving international guidelines for research involving human subjects. These will permit research jointly undertaken between nations and amongst groups of nations using common protocols, stimulate sharing of research results amongst nations and avoid unnecessary duplication and multiplication of research efforts.

The question of how common standards can best be developed and implemented considering the present diversity in practice and the complexity of the biomedical research enterprise occupied much of the discussion.

For that reason, the delegates recommend that, in order to safeguard the rights and well-being of patients and research subjects, research ethics committees should be established in all countries. All research projects involving human subjects must be submitted for approval to a research ethics committee.

It is further recommended that these committees should be comprised of medical experts, and of experts outside the medical profession (e.g. theologians, moral philosophers, lawyers and lay members who represent the general public). Lawyers acting professionally for an institution, and others having a financial interest or potentially conflicting interest in the institution or the research in question should not serve on the ethics committee adjudicating that research. Furthermore, the committees should be of a size which is sufficient to allow for the inclusion of the three groups (medical experts, outside experts and lay members) and small enough to make efficient work possible.

Delegates also considered the means of operation, freedoms and accountabilities of the research ethics committees. The decisions which they must take often reflect fine-tuning of competing values, and the scientific, technical or cultural environments within which they work may vary. Therefore, some differences of views between research ethics committees should be expected. Delegates were of the view that, while there may well be a need for nations to monitor the functioning of local research ethics committees, the highest standards can best be assured if they are given responsibility and authority for the review of research ethics in their institutions; as well, their effect will be enhanced if seen by researchers and society as working with the research process in a collegial sense rather than in an adversarial mode.

3. Sharing the Risks

Three groups in society can be identified as carrying risks and benefits. The researchers or clinicians who carry out the trials and other research carry the primary burdens of ethical responsibility for protection of the research subjects. In the context of drug testing, the risks and costs of developing a new drug or device remain with the manufacturer. Nevertheless, the human beings on whom the research is performed carry the most direct risks of research, but can gain the benefits of the higher standards. Society or mankind as a whole is the ultimate beneficiary from research towards improved health standards, and for that reason, the delegates recommend that human research subjects be fully informed concerning the availability or the lack of availability of mechanisms of care and compensation to subjects who are injured as a result of their participation in research. The delegates encourage member nations to establish and implement appropriate mechanisms for care and compensation in areas where they do not presently exist.

4. Public Participation

The delegates agreed that the imposition of societal standards on the sensitive areas raised by medical research demand the involvement of the general public. Public involvement is required not only in the development of consensus but also in consideration of individual research proposals to ensure full and open discussion which might otherwise be uncritical or too narrowly based. The multi-disciplinary character of research ethics committees provides for both public accountability and credibility.

5. Research with Those with Restricted Ability to Give Consent

The overriding purpose of ethics review is the protection of the research subjects. An essential component of this protection, enunciated in all international codes of ethics, is that each research subject must consent freely, and with full information, to participate in the research. However, those who are legally incompetent cannot, by definition, give their consent. Delegates focused their discussion of this issue on research with children, while recognizing that similar concerns arise with adults who are mentally handicapped and with other vulnerable populations.

All delegates accepted the need for therapeutic research with children. Such research would be of potentially direct benefit to the well-being of the individual subjects.

Non-therapeutic research with children poses special problems. While such research is necessary if treatment of childhood diseases is to advance, there was agreement that such research could only be considered under the following conditions: the specific project must be approved by a research ethics committee; all needed knowledge must have been obtained through research with adults or animals; there must be no valid alternative to the use of children in the research; a valid proxy consent (by family, guardians, ombudsman, those with power of attorney or others) must have been obtained for each research subject; and, to the extent possible, the child should have given assent. Thus, it was the view of most delegates that needed non-therapeutic research on children, if within the limitations just mentioned and if involving minimal or no risk to such children, should not be precluded.

6. Research with Embryos

The integrity and uniqueness of human life in its earliest embryonic stages of formation must be accorded great respect. Generally, current forms of control of research procedures and manipulation of human embryos are not legislative in nature. In fact, in the almost total absence of legislation, research on the embryo is presently, for the most part, governed by the self-regulatory efforts of scientific and professional bodies, the centres themselves, and the review by ethics committees, local and national. Voluntary licensing control exists, for example in England, but there was consensus on the need to regulate the current anarchic proliferation and operation of *in vitro* fertilization centres in some countries as an interim measure while acquiring the experience necessary for effective legislation. Thus the delegates recommended the need to keep in balance the professional liberty for clinical treatment and for scientific inquiry in the interest of progress in medical knowledge and skill while upholding regard for the human interest in the embryo. To this end, the delegates recommend the supervision and control of centres offering *in vitro* fertilization, of related treatments for infertility and of those conducting embryo research. Procedures should be regulated according to appropriate guidelines administered by a competent authority.

All delegates recognized the preciousness of the human embryo. Nevertheless, different positions were taken with respect to the possibility of permitting research on the human embryo.

Several questions were raised with respect to the applicability of legal concepts of "ownership" (more properly discussed in terms of legitimate interest in) and control of human embryos during storage or after the death of the donors. Questions were also raised concerning penal sanction as opposed to professional regulation.

Considering the experimental nature of *in vitro* fertilization, its low success rate and the unknown long term effect of these procedures, which though "therapeutic" in nature for the infertile have implications for the manipulation and control of human life, **any work with embryos even as a treatment for infertility should be regarded as developmental procedures that are experimental in nature and therefore should be closely monitored.**

7. Pilot Studies and the Introduction of Novel Therapies

Delegates debated the special problem of ethics review of pilot studies or preliminary studies of medical innovations. Such studies were viewed as a phase between the initial observations on one or a few patients and the start of a full fledged protocol-based program.

Delegates recognized that it is often not easy to be sure whether an intervention by a physician should be regarded as a treatment undertaken only in the patient's best interest, or whether it is guided also by an intent to gain scientific knowledge.

The decision on when a research intent is present in therapy is a determination to be made by the physician. It was the opinion of the delegates that, if the health professional has any doubt whether the intervention is in fact research, the issue would best be brought to the attention of the ethics committee.

In reviewing the novel therapy of research, delegates recommended that **they should be subject to the same ethical judgements that apply to all research protocols. Special consideration should be given to limiting the number of subjects entered into pilot studies and to monitoring closely and frequently.**

In ethics review of pilot studies as in that of other proposed research, the delegates agreed that provision should be made for a mechanism to re-examine a research project rejected by a research ethics committee if the investigator should request it. Such a mechanism should be of a sort which would not invite the overriding of local decisions by a higher or distant authority. It should maintain the collaborative nature of the relationship between the researcher and the ethics committee, rather than encourage an adversarial relationship. It was also agreed that there should be a greater exchange of information between research ethics committees.

8. Industrial Research

Industries are a major source of medical innovation. Also much of their research is mandated by national standards for licensing drugs or devices. This research involves both animals and human beings and is often carried out in a number

of countries. For that reason, the interactions between industries, governments and sometimes universities are of great concern.

Differences in the way ethics standards are interpreted and implemented can have direct economic effects. Lack of consistency can adversely affect national and commercial interests as well as the safety of research subjects. Delegates recommended that, at the very least, **a nation should not allow or support, in other countries, research which does not conform to ethics review standards at least equivalent to those in force within the nation.** Nations and industries should develop international accords which strive for common attitudes and the exchangeability of standards and for mutual trust. Nations and industries should also identify emerging technologies to foster early discussion of the ethical concerns. Such interaction might help the equitable distribution of effort in research and development.

Delegates also discussed the ethical concerns raised by the growing pace of commercialization of biomedical products. The increasingly close links between university-based and industry-based research mean that academic physicians or institutions may have financial interests in the outcome of the research; any such potential conflicts of interest should be declared in the research ethics review process. Moreover, it was the opinion of some delegates that we should develop and implement values which integrate ethics and economic interests.

Delegates also discussed the effects of confidentiality, and of compensation of research subjects. The confidentiality of commercially sensitive material may not be consistent with the requirements for ethics review. In addition, payment can induce subjects, especially those of more limited means, to participate in research, and may lead to financial competition for research subjects. With respect to both industrial and other research, concern was expressed over whether patients will be compensated for adverse effects which may on rare occasions arise from research.

Much industrial research and other biomedical research depends on research with animals. Delegates recommended that **in all research we must continue to insist that animal research precede research on humans, while recognizing the obligation to reduce the number of animals required to a minimum wherever possible and to encourage alternative methods for assessing safety and efficacy.**

Much of the regulatory testing of new drugs still requires the use of animals. In this regard, delegates recommended that **governmental agencies continuously modernize their own regulatory requirements to ensure that they do not demand test results of safety and toxicology which are no longer relevant or which can be replaced by satisfactory alternatives requiring fewer animals.**

9. The Selection of Research Topics and Directed Research

Researchers consider many scientific, social and other factors when choosing research topics; choices are also made in the context of national policies and systems of support as well as national policies and practices in respect to ethics. In some instances, this results in an apparent imbalance between the research topics being chosen and major global needs for research in fields such as fertility regulation and tropical diseases.

International research programs can provide a successful mechanism to promote and carry out research in those areas which are neglected, sensitive and/or economically unattractive to national researchers. These programs can make extensive use of the international scientific community and can apply high standards of scientific and ethical review to carry out research in the areas of high global priority which are difficult to address on a national basis. Those nations with the means to support research have an obligation to devote some of those resources to the research needs of nations without such means.

The group recommended that research should focus upon the development of knowledge in broad fields of science with the aim of achieving a fundamental understanding of biological processes, even those which might not appear to have direct application over the short or longer term. It is seen as a scientific infrastructure of further advance. It was also recommended that the results of research should be applied as rapidly and as effectively as possible.

Large scale support for narrowly focussed research on specific diseases without the necessary foundation of scientific knowledge was seen as rarely, if ever, successful. Also the failure to implement the results of research for the benefit of mankind has, in itself, serious ethical implications.

10. Towards Improved Ethics Standards: Biomedical Research in an Interdependent World

The last decade has witnessed profound growth in improved communication and common endeavor among nations. As well, movement has begun towards international agreement on research with human subjects.

Delegates are certain that meaningful international agreement is not only possible but necessary, and urge the Heads of States to work toward ensuring that practice accords with principles in all aspects of research involving human subjects.

The delegates accept that society should make the human subject an active and educated participant in a process in which he or she contributes from a sense of basic human altruism and a desire to serve the common good, rather than as a "subject of research" as has sometimes been the case in the past.

The further refinement and expansion of national standards of research ethics with human subjects across political and cultural boundaries demand continuing investigation into the ethical problems of biomedical research. Furthermore, while agreeing on the necessity for this ethical review process, the delegates recommended that these committees themselves, their operations and their functions be studied.

According to the delegates, research ethics should always be integrated into clinical decision making. The delegates recommended that education in medical ethics for physicians, investigators and medical students be intensified and that the media and public be informed.

Delegates also recommended that special attention be given to the ethical issues involved in epidemiological studies which can be as intrusive of human dignity and privacy as medical intervention. In particular, the regulation of confidentiality, which may both restrict the exchange and gathering of information and may at the same time fail adequately to protect the subject of such epidemiological studies, requires examination.

In regard to dissemination of principles, statements by way of declaration are laudable and necessary. However, if such statements are to have proper binding power, they must be known and an effort be made to ensure compliance with them. To assist in this endeavor and in view of the importance of continuing dialogue, delegates recommended the establishment of appropriate fora devoted to the issues arising in research with human subjects.

Conclusions

This conference affirmed the growing importance of international agreement and cooperation on both the elaboration of principle and on the implementation of ethics review processes in medical research involving human subjects. To this end, the establishment of multi-disciplinary research ethics review bodies for the examination of research protocols was considered essential, as was further study and communication among nations.

Implementation of effective ethics review processes demands the enhanced education in medical ethics both of those involved in research and of the greater public.

The development of national and international standards for research with human subjects and their implementation must continue to aim at the protection of more vulnerable subjects.

The promulgation of ethics standards for research across nations and cultures should focus on areas of concern, as well as on international needs that are not being met.

Press Conference

Press question: With respect to research with children, Mr. Justice David Marshall mentioned a majority opinion, I wonder what reservations or minority opinions there were on that particular issue.

M. Jean Michaud: This question of research with children gave rise to a lengthy discussion – a discussion that I would call difficult. The majority opinion expressed in the text was not unanimously recognized by the delegates. It is true that when all other forms of research have been concluded, other forms of research being laboratory research and research with animals, then some forms of research are necessary on human beings. This is true in general terms. I believe in principle that the only time research on children is permissible is with childhood diseases. Research with adult subjects is not possible when one is dealing with diseases of children.

One principle that we all defend is that if research is partly therapeutic, then it could, if it has a wider aim, also be used for humanity as a whole. Another principle is that when research is not therapeutic, when it is purely research for the sake of obtaining information, then this research must definitely not be harmful to the subject. This is all the more true, when one is dealing with fragile, vulnerable subjects such as the mentally disabled, mentally retarded, sick persons and, in this particular case, children. The smaller the child, the younger the child, the more vulnerable.

This is why our Conference has stated that insofar as the child subject runs no risk or only minimal risk, non-therapeutic research, in other words research not designed to cure or treat that child because that child happens to be healthy, can be carried out.

Since the very young child is unable to give consent, it is necessary before any research is carried out to obtain authorization from the child's parents or, if the child has no parents, authorization has to be received from the guardian or ombudsman or other competent person. I believe that the text says that authorization may also be obtained from the Ethics Committee.

As you can see, this position is hedged about with many conditions. Consent has to be obtained from the persons who are competent to give it on behalf of the child, the risk must be minimal at best, preferably no risk at all, the Ethics Committee has to be consulted. Despite all these precautions, one delegation felt that this was still too lenient and that in actual fact, no research should be performed on a child who up to a certain age cannot give consent. Research can be merely taking a blood sample; we are not necessarily talking about invasive research. In the case of let us say a fifteen year old child, one would ask the child's personal opinion while at the same time requesting the authorization of the parents or the other appropriate bodies. However, one delegation felt that it was not possible to go even that far.

Press question: Earlier you said that the final report will be presented by Prime Minister Mulroney at the Economic Summit Conference in June in Venice. Does this mean that Canada entirely supports this report? Secondly, I would like to ask if you

dealt with the obligation of informing persons who are part of an experiment of the dangers that they must undergo?

Mr. Justice David Marshall: To answer your first question, we do not presume to speak for anyone but ourselves. We were delegated by the Prime Minister to look at these questions. We have looked at them to the best of our ability. We have given him our best opinion. I do not think that these opinions are binding on the people of Canada.

To answer your second question on informing people of the dangers of a research project, that of course, is a very vital and underlying issue in our deliberations both in the principles and in the formulation of proper practices. So, we have addressed that issue in some detail.

Press question: In forming Ethics Committees, was it the general agreement of the delegates that this should be the responsibility of the national government of a country and was there a time frame set for when they would be expected to have them set up?

Dr. Charles McCarthy: I think it was the general opinion of most of the delegates that Ethics Committees be established at a variety of levels, at local levels, usually associated with the institution or the research site, at some intermediate levels that might be regional or state or provincial and at national levels. I think that the methods or the procedures that are used to establish these will probably depend on the national character, the way the nation is organized, and the tradition that exists in the country.

In the United States, we have a general law that requires the establishment of committees at every site where research is carried out or supported with federal funds. We have such a system because our country is very large. In order to obtain some kind of uniformity, it needs to be established by law and by regulation. In the United Kingdom which is geographically much smaller and where the delegates or the institutions are often in close contact with one another both personally and geographically, this is done by way of custom. The committees are established, usually with the approval of the Medical Research Council, by local authorities either in the institutions or in the regions. We think that is entirely appropriate for the kind of structure and geographical nature of a nation such as that. There are different conditions in Denmark that we heard about and still others in France and in Germany. It is really left to the discretion of the member nation as to how best to proceed.

I think the majority of nations are leaving it to the discretion of local associations, societies and institutions as opposed to requiring it by the central government. We see variations of this all across the world. The important point, however, is there is general agreement that there must be such committees, they must have wide representation of disciplines, they must include representatives from the public, they must be accountable in some kind of public way so that the public can be assured that the subjects are adequately protected. So those common themes run through the structures in all of the nations represented here. We find that very helpful because as research becomes more internationally structured, these committees if they are not at least reasonably consonant from nation to nation will conflict and perhaps interdict the flow of information from one nation to the other. As a result of this conference I

am going to go back to my country very much reassured that the basic principles on which these committees operate and the fundamental structure of these committees is sufficiently consonant, while not necessarily identical, to allow research and high standards of ethical implementation of research to be universally implemented.

Mr. Justice Marshall: I want to say more about your question on children in research, to tell you what we perceived the terrible dilemma to be. We are of the view that, for solutions to certain terrible diseases in children to be found, it is necessary that some research be done on children which may not be to their benefit. There is a tremendous desire to undertake this vitally important research for the betterment of all children and mankind. On the other hand, children are a very vulnerable population and laws in many countries protect children, of course. The great dilemma is the conflict between the desirability of conquering these terrible diseases and, at the same time, the great importance of protecting children from abuse.

Press question: This question is for Dr. Barzelatto. Are there currently industrial research projects going on in third world countries which are raising concern with the World Health Organization? Do you think that the recommendations here are enough to stem those practices?

Dr. José Barzelatto: Only a very limited amount of industrial research in developing countries has given any cause for concern. The main problem concerning research in developing countries is, however, that developing countries themselves have very restricted capacity to do independent research, and research activities supported by sources in the industrialized countries often do not cover the topics in which these countries are really interested. For example, many tropical diseases do not exist in industrialized countries and hence have not been the major subjects of research. This situation can be corrected only by a concerted international effort, and that is what the report says in this respect. One cannot ignore the fact that 75% of the world's population lives in the developing countries. The research resources of these countries have to be expanded so that they can give proper attention to the problems that concern them. It cannot be expected that solutions to these problems will be developed completely outside and simply transferred there. This I think is the main justification for international efforts.

Dr. Paolo Fasella: Mr. Chairman, perhaps in continuation of what Dr. Barzelatto has said we could draw your attention to an important conclusion concerning both present and future industrial research. The delegates recommend that at the very least no nation should allow or support research in other countries in which the ethical review standards are not at least equivalent to its own. This conclusion affords protection to populations which may be in a weaker position, perhaps because they have not yet elaborated appropriate standards and the technical tools which are needed to implement such standards. This I think is important because it discourages what could become a temptation for some agencies to practice experiments on populations that are not fully protected. This could distort, of course, commercial competitiveness deriving from such research. It is a proper topic to be brought to the attention of the Economic Summit which is generally very concerned, of course, with the well being of people, but also with the rules of fair competitiveness.

Press question: I would like to follow-up on that because there was a bit of equivocation in that explanation. There was an implication that the problem is a current one

as well as a future one. If it is indeed a current problem of companies doing development work in third world countries, can you give us some specific examples?

Dr. Barzelatto: As I said before, there is very little such research. What happens is that foreign companies mostly engage in the introduction of new products rather than in active research. New drugs are provided to local physicians free of charge for testing, and frequently physicians utilize them without following proper research protocols. The physicians' reports on the drugs are then used as test results and in most cases positive claims are made on this basis. In addition, there are a number of products on sale in developing countries which have never been tested scientifically. But usually everything that is on sale in a country has been approved by the government. Thus the presence of such drugs on the market also becomes the responsibility of the governments. Unfortunately, in many developing countries (and even in some developed ones) appropriate mechanisms do not exist for the review of pharmaceutical products prior to authorization for sale.

Moreover, many developing countries do not even have the expertise to do this.

Prof. Albin Eser: As Dr. Barzelatto just mentioned, it is not only a problem between industrialized countries and third world countries, but also within industrialized countries. Quite a few drug tests are carried out in other countries. American drugs, for instance, are tested in some European countries. There are still different standards in different countries, less strict in one country, more strict in others. There might be some tendency to test drugs in countries where the rules so far are not as strict as the home country of the company which wants to market the drug. Perhaps, it might also be a cost problem; it may be cheaper to test a drug in European countries than in the United States. I would like to underline once more what Dr. Fasella said. I think it one of the most important recommendations that no country should carry out a research project in another country if their rules are not at least equivalent to those in the home country of the researcher.

Dr. McCarthy: There is in draft in the United States now a new regulation that will apply to every federal agency that conducts or supports research anywhere in the world. This includes our Department of Defense, our Department of Energy, our Department of Health and Human Services, and many other agencies. We think it is extremely important that we do not carry out research in any nation anywhere in the world that could not be carried out with subjects within our own borders.

We welcome this. Although the Conference resolution is couched in that section of the document that relates to industry, if you look at the careful wording of the resolution itself, it applies to nations as well as to industry. We think it most important that we do not degenerate in our protections for human subjects to the least common denominator. Consequently, requiring standards that are at least equivalent to those that are used in the nation or in the industry in the nation where the industry or the government originates is extraordinarily important for maintaining high standards of ethics as well as high standards of science.

Prof. Gordon Dunstan: May I add that the Council of Europe has recent guidelines giving minimum standards for the control of experiments involving animals? Countries, of course, are at liberty to impose even more strict standards if they wish, but the minimum is laid down. It would seem odd that we have minimum standards for

the experimental use of animals without something equivalent for the experimental use of human beings. Our aim is to meet that gap.

Press question: Part two of the Summary Report states that uniform practices are not widely accepted due to national and cultural differences. Is it correct to assume that the key cultural difference is a religious one?

Prof. Vittorio Sgaramella: Thank you Mr. Chairman. The answer is no. We do not equate culture with religion by any means. We know that religion is an important part of the set of values of our tradition but we have tried to keep a distinction between culture and religion. There was certainly very careful attention to the cultural aspects of the various countries.

Prof. Koichi Bai: I think all the points have been mentioned already. The differences of cultural values have not been neglected. We are here to come face to face with our cultural differences. Despite that fact, there are certain uniform standards that can be established. As was mentioned by Justice Marshall, what we are looking for is to standardize as much as we can. At the same time, we are to pay due respect to the cultural differences. I think that the boundary between the universal and the peculiar is not fixed, but flexible. In other words, what has been considered as universal must be continually reviewed and renewed, taking into account what has been peculiar. At the minimum level, perhaps we can standardize something, but the rest will be left to the differences of the cultural values of different countries.

Dr. Barzelatto: If I may, Mr. Chairman, I would like to present some examples from the Human Reproduction Research Programme for which I am responsible at the World Health Organization. Contraceptive research is an area where one finds striking differences in human behaviour with respect to both culture and religion. Although personally I think that, separate as they are, religion is part of culture. Indeed there are religious beliefs that influence a community's choice of contraceptives, but the choice is also influenced by cultural factors that have nothing to do with religion. This is also true for medicaments. For example, injections may be popular in one country but not in another. The contraceptive pill is so popular in the developed countries, but in many developing countries, particularly in Latin America, many women prefer monthly injections, which are not popular in the developed countries. Such choices are not related to religious beliefs. Rather, they are related to cultural values. A vaginal suppository in some cultures would not be acceptable. Thus, a number of factors other than religion can influence the choice of different methods for contraception as well as for treating or preventing the disease.

Prof. Eser: I want to give two other examples where cultural differences may be important. Let us take the relationship of man and nature and animal. In the western world, we could consider man as master of nature and the animals as the servants of man. We have an anthropologically oriented culture whereas some other cultures consider man and woman only as part of nature, but not as the master of nature. This of course, has an influence on, for instance, how you deal with animals. Another example, more technical, but quite important, refers to the problem of ethical committees. There are certain countries which rely very much on social control as opposed to legal control.

Those countries might be completely satisfied to have control only with ethical committees. In other countries it might be more in their tradition to have state control.

Mr. Justice Marshall: Do you have a further question?

Press question: Coming to the point about compensation for people who are perhaps harmed by research, how would you see that compensation being funded? Through a public agency? Through the companies that do the research?

M. Michaud: I can tell you about the French experience which does not run counter to what is in the conference report. We do not intend to allow the subjects to obtain enough money to live by means of the money they would receive from taking part in the trial. If they were to make a living doing this, their consent, which has to be freely given and informed, might well no longer be free. I think for example of the unemployed. An unemployed person might be able to make a living by offering his body for trial purposes. One can imagine that apart from actual remuneration, compensation could be given to subjects of experiments. In other words, they could receive a sum of money which first of all would compensate them for the inconvenience to which they have been subjected and for the time that they have had to devote to the research and the subsequent loss of income.

Mr. Justice Marshall: Thank you. I might add something about the Canadian position on that. We have just published a working paper on research on human beings in Canada under the auspices of the Medical Research Council. Our recommendation in that document is that the subject be informed if there is no insurance. We assume that there is insurance or the informed consent will be on the basis that the person will be told that. Our approach in the document is that the person is to be told if there is no insurance.

Dr. McCarthy: In the United States, we have no universal coverage for injuries that may be incurred as a result of research. In most of our country health insurance is provided by private insurance companies either through group programs or sometimes through individual insurance policies. Rarely do these policies cover injuries incurred outside of the normal practice of medicine. Rarely do they cover the context of research where the subject may indeed volunteer to participate in the research and where there is an exceedingly low but perhaps measurable incidence of occasional injury and an even lower incidence, but occasional incident of serious injury. Consequently, in the United States, most institutions provide care, but few of them provide any kind of monetary compensation for a subject injured in research. What we are asking here is that, before subjects enter the research enterprise, they understand what degree of care will be provided in the event of an unexpected injury and whether or not insurance is available. We think that principle applies not only in our country, but worldwide. Many other countries have other forms of compensation or insurance. If it is available, the subject ought to know that as well in making a decision whether to enter a research project. We think there are two issues here: one, that there must be informed consent as to the actual situation and two, where possible, in the event of an untoward injury, that care be provided and compensation given if possible, and, if not, at least that the subject be aware of that situation.

Mr. Justice Marshall: Thank you, Dr. McCarthy. Professor Eser.

Prof. Eser: As far as Germany is concerned we have a legal obligation for insurance before testing drugs. In addition, there is also a broad coverage of health insurance. This of course also makes it attractive for other countries to have tests carried out in European countries because if something happens most of it is covered by the normal health insurance. This is another point where we think there should be some international uniformity in order to prevent a new form of "colonization" in drug testing which, I think, would not be in the interest of the world.

Mr. Justice Marshall: Thank you Prof. Eser. Other questions?

Press question: The preliminary report raises a question concerning the legal idea of the ownership of embryos – the control of human embryos during storage or after the death of the donor. You also ask questions about the criminal sanctions to prevent abuse. I do not see any answers to these questions. Can you tell us your thoughts on the matter?

M. Michaud: We were only able to raise these questions. We have spoken about this at length however, here and in our different countries. This issue is a very topical one, but there is an absence of legal facts on this problem. Science moves very rapidly and the legislation in the different countries is much slower than science. Thus the idea of the embryo does not exist in most of the legislation of the countries represented here. As a result, we are currently questioning ourselves, from a philosophical and legal as well as a religious point of view. Answers were given of course in everyone's conscience. Is the embryo a human being? Is it as the French National Ethics Committee said a potential human being? It is only when these questions will be resolved, if they will ever be resolved, that legislation will take a stand on the civil consequences as well as the penalties which will intervene.

Mr. Justice Marshall: Professor Dunstan, might we ask the British position on this very difficult question?

Prof. Dunstan: In terms simply of the law, the legal status of the embryo, as M. Michaud has said, is undefined. We have however, a long legal prescription which grades the moral and legal protection of the embryo and fetus *pari passu* (step by step) with its growth toward maturity. Within that tradition, no doubt when the time comes, if it ever comes, either Parliament or the courts will have to pronounce on the status of the embryo. Meanwhile, we pursue our professional scientific disciplines, within terms of a presumption in favor of the life of the embryo growing as the embryo develops towards maturity; and, with that development, the difficulties of rebutting that presumption grow also. In terms of research with the embryo and its use in therapies for infertility, the presumption is held to be rebuttable in this early state of fluidity when the pre-embryonic cells are not yet committed to specific organs or systems. The claim of the embryo is held to be so little as against the major claims of active life and active research that presumption in its favor is rebuttable in those circumstances. That is the basis of our action. It has not yet been challenged in the courts, neither has Parliament legislated on it. In terms of the law, I hope I have answered your question. There is more to be said of course, not in terms of the law.

Mr. Justice Marshall: Thank you. I wonder if I might turn to Prof. Sgaramella of Italy.

Prof. Sgaramella: In Italy we are facing this problem in a very intense way. We believe from the scientific point of view that at least the commitment of the embryo (and thus of the single cell embryo, the zygote) is to become a human being. The law, accordingly, prohibits any research on the embryo and asks for any and all embryos which are produced *in vitro* to be reimplanted. There are clearly drawbacks in such a legal position but that is what the Italian law demands.

Mr. Justice Marshall: Thank you. Prof. Eser.

Prof. Eser: As you may realize from the discussion here and the different points of view, this of course, has also been a very touchy problem. So far I think it is fair to say that there is no country where you can really talk of a solution which would satisfy all sides as to the status of the embryo, the protection of the embryo, and research on the embryo. Of course, in embryo research you have to consider the interest of the woman who wants to have a child. You have to consider the life of the new hypothetical child and perhaps you have to consider the sacrifice made for developing and improving new *in vitro* fertilization techniques. I could state as at least a rather broad conviction in our meeting that there should be fundamental respect for the embryo and, as far as I am concerned, this does not necessarily depend on defining the embryo. The main question is whether a human life entity which comes from human sperm and a human egg is valuable enough to be protected, not to be given to the free disposal of anybody. I think there has been a clear conviction here that the embryo has to have protection. So far we have not found, nor I think has any nation in the world, really found a satisfying solution which would consider all the divergent and conflicting interests involved.

Prof. Dunstan: As has just been said, the definition of law is not the end of the story. Let us look at the problem we have to face. The desire for children is natural and deep. Normally nature meets that desire very well. But sometimes nature fails in two respects. It leaves some couples infertile and sometimes it produces a handicapped, malformed child. History is littered with attempts to remedy those two troubles. Now thanks to fundamental, biological research in the human realm, we think we are developing rather more effective methods of tackling both problems. At the moment, both methods are in their infancy and both are highly unsatisfactory in terms of results. It is the beginning not the end. That is first.

Secondly, we have now *in vitro* fertilization and so on. But consider how many embryos were lost in the experimental production of Louise Brown. The life of that child was not achieved without extensive embryonic loss and necessarily so. The moral question now comes. May we, in our attempt to perfect or improve what has been begun, may we still cause embryonic loss? May we sacrifice human embryos composed of the germ cells of human gametes in the abstract, in terms of improving the prospects of a child for particular couples or improving the prospect of a wholesome child and not a handicapped one? That is the fundamental question and it becomes a moral question because never in these fields can we read off an absolute rule of practice from one simple principle. We have here a cluster of principles, each exerting its own claim and we have to reason our way through.

Now some people say we are never at liberty to use human embryos experimentally for any end outside of themselves. The respect for the human being begins at the moment of fertilization and must be as extensive as respect owed to one another of us in

adult life and protected as such by the law. There are difficulties in maintaining that view, but it is maintained and authoritatively proclaimed and conscientiously held.

On the other side, are those who accept, as I indicated just now, that we begin with a primary respect for and indeed awe for the human embryo because each of those cells is packed with a human interest. Our humanity is in those cells whether in fact they emerge as a human being or divert into some carcinoma, or become the part of the placental membranes discarded at birth. But from the beginning the possibility, the prospect of our humanity is there. Therefore, no one within responsible embryonic research or fertility control is lacking in respect for the human embryo. But it is claimed that just as real is the moral demand of satisfaction of the desire for children and the moral obligation not to bring handicapped children into the world if we can prevent it by licit and moral means. Those two legitimate claims can be held to outweigh the legitimate interest which might be held in the embryo to be left undisturbed. Now in therapeutic practice and in the obligatory medical research upon embryos, always there must be this balance of claims.

And that is why lastly, in our recommendation, we have said that while there is a duty to pursue properly conducted research in this field as well as proper therapy, it must be under control. The form of that control will vary from country to country. That is why we have not made any definite prescription for the form. But the principle of control is inherent in our respect for two human obligations: one to respect human life to the utmost; two, to respect the human obligation to exercise our rational nature in means of inquiry and mounting means to do our duty to living human life as well as to its potential. I hope that shows you the depth of the problem we have tried to tackle and, in one sense, both the firmness and the inconclusiveness of our discussion and above all our recommendation.

Mr. Justice Marshall: Thank you, Professor Dunstan. M. Michaud.

M. Michaud: I apologize for asking the floor once again on this issue, but it is such an important one that I think it is worth while. Professor Dunstan a moment ago referred to the respect for the embryo. In practice, at the present time, there are two ways of respecting the embryo, which is so fragile, far more fragile even than the children I referred to earlier and whose fragility and vulnerability in some cases precludes any research on them. As I say, there are two ways of respecting the embryo at the present time. One can say that nothing is to be done on the embryo without the consent of the woman who gave the ovum and the man who gave the sperm. The second form of respect, which I would call administrative, is the control by the public authorities of artificial fertilization centres and embryo research centres where such centres exist. In other words, the centres should be accredited and continuously monitored.

Mr. Justice Marshall: Thank you. Professor Sgaramella of Italy.

Prof. Sgaramella: We have been considering this problem with the attention it deserves. I think we came also to a third form of respect for the embryo which is due to its human nature. We have appreciated the fact that it is very hard to use a human being and to sacrifice him/her in order to cure a disease affecting other people. I think it is extremely important to keep this point clear in our minds. If we use a human embryo for research and we kill the embryo, we are killing a human being in or-

der to cure another human being. That is, I think, a tragic paradox which we cannot ignore.

Mr. Justice Marshall: Thank you, Professor Sgaramella. Other questions?

Press question: What would you anticipate is going to happen to this report once the Summit leaders have a chance to read it and digest it?

Mr. Justice Marshall: The great benefit of our deliberations and our papers and the fine discussion we have had (the quality of which you have seen this morning, I think), in my view, is that each of us has learned a great deal from the experience of others and from the practices of others. Our purpose was to improve through mutual exposure and experience. I do not think there is any other way. We hope the heads of state who get the document will consider the points that we raised. It is certainly of great benefit to us, speaking as a Canadian, to see the practices and ways of handling problems in other countries.

Dr. Fasella: I would like to address the representatives of the press themselves about one point. An important aspect of the report is public participation. The basic concept is that, as the debate has shown, one needs a consensus, a consensus which of course involves physicians, lawyers, philosophers, etc. and which must involve the public at large. One very important element of this consensus is that the proper information, both concerning the scientific and technological aspects and what they imply, but also the current debates like the one we are having here in your presence, stimulated by your presence. I think that one important recommendation which can be a significant follow up of this conference is that the awareness of the press, as one of the most important means of sensitizing public opinion, be further attracted to these problems and become more involved. It is clear that not all problems have been solved. Actually, perhaps more questions have been raised than settled. In this continuing dialogue, the information of the public is very important and the press has an irreplaceable role. Thank you.

Mr. Justice Marshall: Thank you. Dr. Barzelatto.

Dr. Barzelatto: I would like to mention an indirect important consequence of this meeting, that is the fact that the conclusions here will be a very valuable input into other fora which are organized on a broad international basis. The World Health Organization has a long tradition in collaboration with the Council for International Organizations of Medical Sciences of organizing meetings to stimulate the necessary dialogue to come to a consensus on the basis of mutual respect of different values on issues of bioethics. That is a continuing process. In fact, we are planning several meetings with worldwide representation, including for next year a conference on ethics and human values in family planning. It will deal both with contraception and with infertility and hence, with very basic important principles that we have been discussing here.

Mr. Justice Marshall: Thank you. I might just say in the Canadian context, I would agree with Dr. Fasella. Decisions in Canada are made at our local research ethics boards. Conference documents and the thoughts we have discussed here will go to those people who play a great part in decisions at the front lines, so to speak.

Prof. Bai: I wish to make one supplementary comment. It is my view that it is all right to emphasize the differences of the different countries. It does not mean that universalities are being neglected or ignored. It helps to enrich all the quality that is offered by the world. However, here comes in a concretely difficult problem as was mentioned by Dr. Law. Of course, to a certain extent, compromise will be needed. What kind of compromise we choose is something which we have to decide. However, we have also to agree upon the minimum standards about which we must reach some kind of compromise. The minimum standard is that no country should carry out research in other countries in which the ethical rules are not at least equivalent to its own.

In this context I believe this conference was quite fruitful. As was mentioned by Dr. Fasella, let us continue this dialogue, not confining the results to this conference only. Let us continue to criticize each other and to exchange views further into the future. Thank you.

Prof. Eser: May I offer just one more comment on the importance of a summit conference like this? As far as I can judge from the participation at a conference of this sort, there are different addressees. First of course, are the prime ministers of our countries and hopefully, they will endorse what we recommend here. Since the recommendations and the report are published and hopefully, also read by other people, there are quite a few recommendations which do not need any support by the state legislature but which should be implemented by medical sciences organizations. For instance, if we turn to our strong endorsement for improving ethical committees, this has nothing to do with the governments, but with the medical associations. There are still some countries which are reluctant to install ethical committees. We hope that our recommendation in this area as the consensus of an international summit conference will give it some support and moral endorsement. You should see not only the prime ministers as the primary addressees, but also other people who have to carry out rules of protection for human subjects.

Mr. Justice Marshall: Thank you, Prof. Eser. Dr. McCarthy.

Dr. McCarthy: I think one of the very powerful effects of a report of this kind is to document progress. For nearly twenty years, I have been involved with both national and international groups in struggling with problems of this kind. I am getting old enough to realize that enormous progress has been made. We have focussed this morning on many differences that still remain. I presume that the more we explore these issues the more questions will arise. It may never be that we will have universal agreement on these fundamental questions that affect human life, human dignity, the relationship between the general public and the professions of medicine, nursing, law, and other professions. Nevertheless, when I first entered this field, there was very little consensus about such matters as informed consent. There was not even a uniformly accepted view with respect to acceptable risks in research, even for adult and competent subjects. The review committee was the exception rather than the rule, even in industrialized nations. Within a period of approximately twenty years, we have seen enormous growth toward consensus in major parts of the world on all of these points. Each of these meetings has contributed, some in small ways, some in major ways, to this advancement. I think the quality of discussion and the sensitivity of the recommendations of this group are particularly important. Consequently, although they may not have binding force either in Canada or in the other member na-

tions, I think they will have weight by their own intellectual force, as well as by the influence of the delegates who take these back to their respective countries, not only the recommendations but the rationale behind them. I think this report is likely to be considered as extraordinarily important when we look at it perhaps, five, ten, or twenty years hence. I hope I will be around to look at it at that time and be able to give you an assessment of what the historical importance of this document was. At least it is my sense that I have been privileged to participate in an historical advance in the safeguarding of human rights and welfare. For that I am very grateful.

Mr. Justice Marshall: Thank you, Dr. McCarthy. Any other questions?

Press question: Because of this report is there any need for any changes in legislation in Canada? Do we have everything covered by Ethics Review Committees now? Also, does the consensus on the recommendation about human embryos require a change in Canada?

Mr. Justice Marshall: I do not think that one could say that everything is covered. We in Canada are fortunate in several respects. We have a strong, ongoing research ethics review committee system. The Medical Research Council has taken the leadership role in this some years ago in producing guidelines which have been widely followed. There is certainly no consensus on the question of the use of embryos in research in Canada, in our view. We have a very active standing committee on the ethics of experimentation including the use of human beings as research subjects. We have, as I said earlier, produced a working document which deals with that subject. There is no evidence of the growth of centres that are working outside the system of guidelines that we have in Canada. In the working paper you will see that we have accorded the embryo the highest level of respect as a life form. We believe that we have taken a most careful and conservative view. We have limited the use of the embryo to therapeutic situations. In Canada we have a strong tradition of therapeutic freedom in that the doctor and the patient can choose the course of therapy that is best for the patient. The terrible dilemma was outlined most eloquently by Prof. Dunstan. I cannot better that quite frankly. Our guidelines are now, as I have said, in working paper form. These are being reviewed. They have been widely distributed across Canada. They have been available to the public. The public has been invited to comment on them as well as all the agencies that deal in these questions. In my view, the situation in Canada is certainly being most carefully and most seriously considered. Other questions?

Prof. Eser: Since there seem to be no more questions, I think it should be made known to the Canadian public that this conference was very well organized. As a member of a foreign delegation, we are very grateful for all that was done here. We thank you very much for organizing and conducting this conference which was performed in a very good spirit. We hope that this spirit will be carried out and carried on to other parts of the world. Thank you.

Mr. Justice Marshall: Thank you very much, gentlemen and ladies. It has certainly been an honour for Canada to host the conference. It has been a great honour to work with such people as yourselves and to discuss the very serious and important topics. Once again may I extend my special thanks to Judith Miller for her fine work in all aspects of planning and organizing this meeting. On behalf of the Medical Research Council of Canada and the Department of National Health and Welfare, who undertook the conference, I thank each and every one of you again.

Appendix 1: Resumes of the Delegates

Prof. Koichi Bai was Professor of Law at Tokyo Metropolitan University and Professor as well as Director of the Institute for Medical Humanities at Kitasato University from April 1987. His specialties are civil and Medical Law. His publications have dealt with topics such as medico-legal approaches to the concept of death, medicine, law and ethics, and medicine and human rights.

Dr. Zbigniew Bankowski has been Executive Secretary of the Council of International Organizations of Medical Sciences since 1975. Here he directed the preparation of International Guidelines for Research Involving Human Subjects and Animals. His research background is in pathology and histochemistry.

Dr. José Barzelatto is Director of the Special Program of Research Development and Research Training in Human Reproduction of the WHO. A physician and endocrinologist, he has specialized in the management of international research programs, both for WHO and for the Organization of American States.

Dr. André Boué is a Professor in the Faculty of Medicine of the University of Paris. His fields of interest center upon fertility, fetal pathology and research involving the fetus and the embryo.

Dr. Henri Bricaire is a member of both the Royal Academy of Medicine of Belgium and of the National Academy of Medicine of France. His medical career has followed essentially a clinical direction. His fields of interest have been pathology and endocrinology.

Prof. Gordon Dunstan is Chaplain to Her Majesty, the Queen of England. He is also Professor Emeritus of Moral and Social Theology at King's College, University of London and Honorary Research Fellow, University of Exeter. He chaired the working party on reproductive technologies of the Council for Science and Society and serves on the Voluntary Licensing Authority to implement recommendations of the Warnock Commission. He has written on such topics as ethics, duty, consent in medicine.

Prof. Dr. Albin Eser is Director of the Max-Planck Institute for Foreign and International Criminal Law in Freiburg/Breisgau. His publications deal mainly with criminal law and its relation to ethics, focusing on topics such as suicide and euthanasia, sterilization and abortion.

Mr. John Fairclough is the British government's Chief Scientific Advisor. He is the Director of Manufacturing and Development for IBM UK and Chairman of IBM UK Laboratories. He is on secondment from IBM UK to develop science strategies for the British government.

Dr. Liborio Falanga is a lawyer by training. He is currently with the Office of Study and Legislation of the Ministry of Health. His work includes consideration of issues relating to organ transplants, as well as dealing with criteria for the definition of death.

Prof. Paolo Maria Fasella is Director General for Research, Science and Development and is head of the Joint Research Centre of the EEC in Brussels. He is the European Community's representative in the Eureka Group. Prof. Fasella has worked extensively in the field of biotechnology and is especially interested in viral proteins and clinical tests.

Dr. Henry Friesen is Professor and Chairman of Physiology and Professor of Medicine at the University of Manitoba. He has contributed extensively to the field of endocrinology. He is on the Executive of the MRC and a member of the Standing Committee on Ethics in Experimentation of the Medical Research Council.

Dr. Evangelos Garelis is a physician specializing in neurology and psychiatry and is currently the Vice-President of the National Drug Organization of Greece. He is also the Director of the Department of Psychiatry at Athens General Hospital where he holds both clinical and teaching positions.

Dr. Shigeaki Hinohara is President of St. Luke's College of Nursing in Tokyo as well as being a Consultant in Graduate Medical Education of St. Luke's International Hospital, and Chairman of the Life Planning Center, Tokyo. Dr. Hinohara is a member of the Ad Hoc Committee on Life Sciences and Mankind of the Council for Science and Technology, Science and Technology Agency.

Sir Raymond Hoffenberg is the President of the Royal College of Physicians of London, a Professor of Medicine at the University of Birmingham, a Senior Scientist of the MRC Clinical Research Centre, as well as a member of the Medical Research Council (U.K.). His research field is endocrinology.

Prof. Per Juul is the Chairman of the Drug Registration Board of the Danish National Board of Health, as well as being a member of that Board's Adverse Drug Reactions Committee. He is the Chairman of the Danish Society for Toxicology and Pharmacology and a member of the Toxicology Steering Committee of the European Science Foundation.

Dr. Abbyann Lynch, a philosopher, is the Director of the Westminster Institute for Ethics and Human Values. She chairs the University of Toronto's Policy Committee on the use of Human Research Subjects. She has, amongst other committees and task forces, served on the Canadian Institute for Advanced Research Moral Values Task Force.

The Hon. Mr. Justice T. David Marshall is a Supreme Court Justice of the Northwest Territories and Justice of Appeal of the Northwest Territories and the Yukon. Dr. Marshall, also a physician, is Chairman of the Medical Research Council's Standing Committee on Ethics in Experimentation. The Committee is responsible for preparing new guidelines for the ethics of research with human subjects.

Prof. Dr. Gustav-Adolf Martini is Professor Emeritus at the University of Marburg, where he was Director of Marburg University Clinic. Prof. Martini is a member of several international medical associations, as well as co-editor of several leading medical journals.

Dr. Charles McCarthy is the Director of the Office for Protection from Research Risks of the National Institutes of Health. Previously he was Staff Director of the Ethics Advisory Board for Health, Education and Welfare. He is also the Chairman of the Inter-agency Co-ordinating Committee for the Protection of Human Research Subjects.

Mr. Jean Michaud is a member of France's National Consultative Committee on Ethics and Counsellor to the Supreme Court of Appeal. His interest in public and civil law is evident in the positions he has held; Examining Magistrate, Deputy Inspector-General of Legal Services, and Vice-President of the Court of Conflicts.

Prof. Dr. Gunther Patzig has studied classic philology and philosophy. He is a Professor at the University of Göttingen and Director of the Philosophic Institute. He is a member of the Göttingen Academy of Sciences and has published works on Aristotle, logic, ethics and metaphysics.

Dr. Russel Patterson is Professor of Neurosurgery at Cornell University Medical College. He is Vice-Chairman of the American Medical Association's Council on Ethical and Judicial Affairs. He has published extensively in the area of neurosurgery.

Dr. Edmund Pellegrino is Professor of Medicine and Medical Humanities at Georgetown University and Director of the Kennedy Institute of Ethics. Besides his scientific articles, he has written many general articles on medicine, medical education and philosophy.

Prof. Vittorio Sgaramella is Professor of Molecular Biology in the Department of Genetics and Microbiology of the University of Pavia. He is interested in genetic engineering and biotechnology and has worked extensively in the area of risk assessment.

Monsignor Elio Sgreccia is the Director of the Centre for Bioethics at the Faculty of Medicine at the Università Cattolica del Sacro Cuore. He is a member of the Commission of the Ministry of Health on Genetic Manipulation. His basic interests are in the principles of bioethics, including their application in transplantation and euthanasia.

Mr. Eiji Suzuki is President of Mitsubishi Chemical Industries Ltd. He is a member of the General Committee of the Economic Council of the Economic Planning Agency. He is also Chairman of the Research Association for Biotechnology, Chairman of the Life Science Committee of the Federation of Employers' Association and President of the Bioindustry Association. He is a member of the Bioethics Committee of the Japan Federation of Medical Doctors.

Order Form: Papers and Discussants' Comments

The following papers and discussants' comments from the 1987 International Summit Conference on Bioethics are available free of charge upon request. Please indicate which papers you wish to receive and send your request to:

Ms. Judith Miller
Bioethics Summit Conference Coordinator
Medical Research Council of Canada
Jeanne Mance Building, Room 2030
Tunney's Pasture
Ottawa, Ontario
CANADA K1A 0W9

Session C: Underlying Principles for Biomedical Ethics Review of Research with Human Subjects

1. Elio Sgreccia. *Guiding Principles in Biomedical Research*.(*)
Discussant: Gunther Patzig
2. Per Juul. *Sharing the Risks: the Management of Research*.
Discussant: Vittorio Sgaramella

Session D: Development of National Ethics Standards for Research with Human Subjects

3. Paolo Fasella and Umberto Bertazzoni. *Who Sets Standards for What and How*.
Discussant: Liborio Falanga
4. Gordon Dunstan. *The Role of the Public*.
Discussant: Abbyann Lynch

Session E: Procedures in Implementing National Standards for Research with Human Subjects

5. Raymond Hoffenberg. *Mechanisms of Ethics Review*.
6. Vittorio Sgaramella. *Accountability of the Ethics Review Process*.
Discussants for 5 and 6: Charles McCarthy
Shigeaki Hinohara
Henry Friesen

Session F: Issues Relating to Consent

7. Russel Patterson. *Research with Those with Restricted Ability to Give Consent*.
Discussant: André Boué (*)
8. Albin Eser. *The Question of Research with Embryos and Fetuses*.
Discussant: Gordon Dunstan

Session G: Areas of Special Concern

9. Henry Friesen. *Ethics Review of Pilot Studies and the Introduction of Novel Therapies*.
Discussant: Evangelos Garelis
10. Eiji Suzuki. *Ethics Issues in Industrial Research*.
Discussant: Per Juul
11. Zbigniew Bankowski, J.F. Dunne, S.S. Fluss. *Ethics Standards for Research across Nations and Cultures*.
Discussant: Edmund Pellegrino

Session H: Ethics of Choice of Research Topic

12. José Barzelatto. *The Selection of Research Topics and the Effectiveness of Directed Research for International Needs*.
Discussant: Henri Bricaire (*)

Session J: Biomedical Research Ethics in an Interdependent World

13. Jean Michaud. *The Transferability of Systems of Ethics Review*. (*)
Discussant: Koichi Bai
14. Abbyann Lynch. *Possibilities for Refinement and Expansion of Transnational Standards*.
Discussant: Gustav-Adolf Martini
15. Appendix A: A Bibliography illustrating the U.K. Approach to Bioethics

(*) An asterisk indicates that the text is in French.

Please send me the following papers and discussants' comments from the International Summit Conference on Bioethics, April 1987.

- | | | |
|-----------|-----------|-----------|
| 1. _____ | 2. _____ | 3. _____ |
| 4. _____ | 5. _____ | 6. _____ |
| 7. _____ | 8. _____ | 9. _____ |
| 10. _____ | 11. _____ | 12. _____ |
| 13. _____ | 14. _____ | 15. _____ |

I would also like the summary volume of the Proceedings:

Yes _____ No _____

If "yes", which language would you prefer:

English _____ French _____

My return address is: (please print or type)
